

FROM THE CHILDREN'S CLINIC OF THE UNIVERSITY OF HELSINKI (CHIEF:  
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# ON HEMORRHAGES OF THE MEDULLA OB LONGATA AND THE PONS AND ON RESPIRATORY DISORDERS IN PREMATURE INFANTS

BY  
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ACTA PÆDIATRICA, VOL. XXXVII, SUPPLEMENTUM I

*Helsinki 1949*

*Printed in Finland by  
Kauppalehti Oy:n Kirjapaino  
Helsinki 1949*



MED

Sufrag. 73-77 MAY 2 1949

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Almqvist & Wiksell's Boktryckeri Aktiebolag  
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# ACTA PÆDIATRICA





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## P R E F A C E

The investigation described herein was started in early 1939 and a large part of the study material had been collected by September of that year, when the outbreak of war caused an almost continuous interruption in the work, lasting till the beginning of 1945. The latter part of the material was collected in 1946 and the first months of 1947. Most of the cases emanate from the Children's Clinic and the First and Second Women's Clinics of the University of Helsinki and a few cases from the Midwives' College in Helsinki and the children's ward of the Helsinki Municipal Epidemic Hospital.

In presenting the results of these studies I wish to express my appreciation and gratitude to Professor A. Ylppö, M.D., Chief of the Children's Clinic, upon whose suggestion the investigation was started and who in the course of years supervised the work and followed its progress with unfailing interest. I am also deeply indebted to Professor A. Saxén, M.D., Chief of the Department of Pathologic Anatomy in the University of Helsinki, under whose guidance I carried out the pathological examinations.

My thanks are due to G. Wangel, M.D., Assistant Doctor in the Department of Pathologic Anatomy, for advice imparted by him. I also wish to thank C.-E. Räihä, M.D., Assistant Chief of the Children's Clinic, for assistance in dealing with physiological questions.

I extend my grateful thanks to Professor M. Rauramo, M.D., Chief of the First Women's Clinic, to Professor A. Turunen, M.D., Chief of the Second Women's Clinic, to Professor A. Apajalahti, M.D., Chief of the Midwives' College, and to Professor V. Rantsalo, M.D., Chief of the Helsinki Municipal Epidemic Hospital,

*for kindly permitting me to study cases in the hospitals supervised by them.*

*I also thank my colleagues at the Children's Clinic for assistance rendered to me in various ways.*

*Finally I thank Miss E. Kaukokallio, who has translated this report into English.*

*Financial contribution toward this work has been granted by the Finnish Medical Society "Duodecim" and the Research Foundation for Children's Diseases, which I gratefully acknowledge.*

*Helsinki, May 1948.*

*Mikko Hirvensalo*

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# I

## INTRODUCTION

### EARLIER INVESTIGATIONS ON INTRACRANIAL HEMORRHAGES IN NEWBORN INFANTS

In the early nineteenth century reports on cases of hemorrhage in the brain of newborn infants were published by Denis (1826), Billard (1828) and Cruveilhier (1829—1835). Cruveilhier already reached the conclusion that intracranial hemorrhage is the cause of death in about one-third of all infants dying during or immediately after delivery. Studies on these hemorrhages in infants were also published in the latter half of the century by Virchow (1851), Little (1862), Gowers (1876), MacNutt (1885), Kundrat (1891) and others, but it was not until the opening decades of the present century that intracranial hemorrhages of the newborn were made a subject of continued and intensive study. The numerous investigators dealing with this question include gynecologists, such as Seitz (1907), pathologists, among others Beneke (1910) and Schwartz (1921—1927), pediatricians, Ylppö (1919), Catel (1928), Brander (1937) and others, and neurologists, as Zappert (1926, 1935). Otological studies have been carried out among others by Voss (1923) and Berberich and Wiechers (1924), and ophthalmological investigations by Stumpf and Sicherer (1909), Stocker (1927), Richman (1937) and others. In recent years birth traumata and intracranial hemorrhages of the newborn have been presented in studies by, among others, Kehrer (1939), Pfaundler (1941), Alpers (1943), MacGregor (1946) and Baar (1946).

The results obtained by the different investigators show great variance, depending upon the method employed, the accuracy of the observations, and the type of material. It has been stressed that an accurate identification of infantile intracranial hemorrhages demands great competence and care on the part of the investigator. Esch (1916) states: "Tödliche Blutungen werden öfter übersehen als zu Unrecht angenommen." The stage of development and age of the infant also influence the results. Premature infants in particular show a remarkable tendency to hemorrhages (Ylppö). As the newborn infant grows older the number of positive findings of traumata decreases and these are supplanted by others arising from extrauterine life, such as infections of the respiratory or alimentary tracts (Saxl, 1935, Pfaundler, et al.). Roberts (1939) is of the opinion that intracranial hemorrhage generally is a direct cause of death only within the first three postnatal days. Variance in the autopsy findings may therefore arise also because of different origin of the material, i.e. a maternity hospital or a pediatric hospital (Pfaundler). Further the results may be influenced by the interpretations of the dissector. It is therefore not surprising that variations of from 2 to 90 per cent exist in the incidence of intracranial hemorrhages in autopsy findings on newborn infants (Pfaundler). According to Kehrer the incidence of intracranial hemorrhages in the various materials examined in the investigations made within the last few decades ranges from about 25 per cent to about 50 per cent, being generally about 30 per cent of all neonatal deaths. This comprises both fullterm and premature cases.

Apart from intracranial hemorrhages, bleeding has also been encountered in numerous cases in the spinal cord and its environment (Ylppö; Hausbrandt and Meier 1936; et al.).

The high incidence of intracranial hemorrhages has also been proved by ophthalmological and otological studies. Thus Stocker found that the incidence of retinal hemorrhages in the newborn generally varies from 10 to 34 per cent in the materials of the various investigators. This author examined for retinal hemorrhages twenty-two infants delivered by Cesarean section but did

not find a single case of such hemorrhage. In 498 infants examined within 48 hours after birth McKeown (1941) found rapidly resorbing retinal hemorrhages in 42 per cent of the cases but none in ten cases delivered by Cesarean section. The cause of retinal hemorrhages in the newborn infants is most generally assumed to be venous stasis produced by the increased intracranial pressure at parturition. These hemorrhages are the more frequent the longer the duration of the delivery. So for instance in cases where the delivery lasted less than six hours retinal hemorrhages were encountered in 28.1 per cent, in deliveries of from 12 to 18 hours in 50 per cent, and in those lasting from 30 to 54 hours in 100 per cent of the cases (McKeown). In connection with retinal hemorrhages a number of investigators have studied the benefit derived from a prophylactic vitamin K therapy. Wille (1945) reports retinal hemorrhages in 42.2 per cent of the cases in which no vitamin K prophylaxis had been administered to the mother and in 31 per cent of the cases in which this had been done during pregnancy or delivery. According to this author minute hemorrhages in the newborn disappear within three or four days and therefore findings may vary according to the age of the infant at the time of examination.

Among otological findings should be mentioned those made by Voss, who in studying the effect of birth traumata upon the auditory organs of infants under four weeks of age observed in 30 histological examinations of the petrous bone a heavy congestion of blood and an abundance of hemorrhages in, among other areas, the region of the internal ear and of the petrous bone in nearly all cases.

The early investigations on cerebral hemorrhages of the newborn were focused mainly on fullterm cases. The theory was generally held that the death of premature infants is caused by their incapacity to sustain extrauterine life due to a general weakness of the premature organism, so-called "Lebensschwäche" (Rommel 1907, Bumm 1917). Autopsies on premature infants therefore were not generally considered necessary in maternity hospitals, where their care was mainly centered (Lesser 1910).

Nonetheless certain references to such autopsies appear already in the literature of the nineteenth century. Thus for instance Billard, in speaking of findings at autopsies performed on the newborn, also reports observations on premature cases. Miller (1886) gives similar information. Mention should further be made of Wallich (1898) and Fahr (1910), both of whom describe cases of ecchymosis encountered in premature infants, and of Freud (1890), who stresses the part played by prematurity in the causation of cerebral birth traumata. Reports on postmortem examinations of premature infants also were published in the field of medical jurisprudence (von Hofman 1891, Knapp 1898, et al.).

Of fundamental importance in the study of premature cases are the investigations carried out by Ylppö (1919). His observations include the ascertainment of a remarkably great tendency to hemorrhages in premature infants. A notably large number of hemorrhages caused by birth traumata were encountered in the region of the central nervous system in particular. They occurred in 76.5 to 90.0 per cent of premature infants of the smallest size, in 35.3 per cent of those weighing 1,501 to 2,000 g., and in 26.7 per cent of those weighing 2,001 to 2,500 g. Subsequent studies by numerous investigators have confirmed this statement on the incidence of intracranial hemorrhages in premature cases. So e.g. Schwartz reports, according to Kehrer, intracranial hemorrhages in 65 per cent of all stillborn infants or those dying under the age of five months, and Weiss (1925) in 20 per cent of the infants weighing less than 2,500 g. at birth. In a material collected by Sunde (1930) consisting of 200 children dying of intracranial hemorrhage during delivery or as newborn, premature cases comprise 60 per cent of the total material. Autopsies made by Nevinny (1936) on 30 infants not over eight days old and with birth weights from 1,501 to 2,500 g. revealed intracranial hemorrhages in 50 per cent of the cases. According to Browne (1921), intracranial bleeding occurred 16 times more frequently in premature infants than in fullterm babies. Among 618 cases of neonatal death MacGregor identified intracranial hemorrhage as the cause in 171 cases or in 27.6 per cent; of these cases 81.8

per cent were premature. Mention should also be made of Paul (1900), who in examining the fundus of the eye of 200 newborn infants established hemorrhages in 20 per cent of the cases; in the premature infants of the series hemorrhages were encountered in 40 per cent. In a material of 458 newborn children Edgerton (1934) found retinal hemorrhage in 25.7 per cent; in the premature infants hemorrhage was present in 50 per cent of the cases.

#### RESPIRATORY DISORDERS AS CAUSE OF NEONATAL MORTALITY OF PREMATURE INFANTS

Neonatal mortality, i.e. deaths within the first days and weeks of life, which total about 2 to 3 per cent of all live births (Salmi 1944, Woolf 1946), comprises for the greater part premature infant cases. Calculations made by Räihä (1940) on material collected from the Women's Clinic of the University of Helsinki indicate that one-half of all stillborn children are premature and that these infants constitute 80 per cent of the neonatal mortality. In material from the same clinic Brander (1942) found 1,475 live premature births in the period 1919—1927. A total of 813 of these premature children, equal to 55.1 per cent, died before the age of 15 years. Of these deaths 53.8 per cent occurred within the first 24 hours, 62.3 per cent within the first five days, and 83.1 per cent within the first month. In the different materials reported in the literature the share of premature infants in newborn mortality varies from 60 ja 80 per cent (Alexander 1937, v. Sydow 1941, Salmi, Ylppö 1942, MacGregor, et al.).

It is well known that, in general, the smaller the birth weight of the premature infant the lower the viability of the child. In Ylppö's material (1919) the rate of mortality within the first month after birth was 83.8 per cent for premature infants weighing 1,000 g. or less, 48.1 per cent for those weighing 1,001 to 1,500 g., 23.8 per cent for those weighing 1,501 to 2,000 g., and 14.9 per cent for those weighing 2,001 to 2,500 g.

Apart from the stage of development of the child, also numer-

ous other factors may contribute to the premature infant death. In the early days *debilitas vitae* was regarded as a sufficient cause of death. Later Ylppö indicated a number of pathological changes typical for premature infants, among them hemorrhages, and therefore birth trauma, in particular intracranial injury, was regarded as playing a very important part among the causes of neonatal death in premature cases. A large number of other causes originating in the mother or the child also have been described as leading to the death of the premature infant, such as intrauterine injury to the fetus due to diseased conditions of the mother, congenital defects in the development of the child, asphyxia, immaturity of the respiratory center, infections of the child, and other causes (Ylppö 1931, et al.). External conditions, for instance thermal and other procedures of care of the premature infant also have a marked influence, an example of which is given by the statistics compiled by Dunham (1936) on the basis of material from 100 American hospitals, in which the premature infant mortality rate varies from 18 to 94 per cent.

It is a recognized fact that *premature infants generally have a tendency to respiratory disorders* and that a large percentage die following more or less manifest disturbances of this kind. It is stated for instance by Peiper (1937): "Die zentralen Atemstörungen der Unreifen bilden die häufigste und gefährlichste Hirnkrankheit des Menschen." Many investigators see in these respiratory disorders the true cause of death of the infant, and numerous theories have been presented in an effort to shed light upon the question.

When a child is born into the world at term, its respiratory process is not as yet fully similar to that of the adult but is deficient at first, and the inspirations and expirations may be irregular or periodically variable (Smith 1946). The interchange of air, which at first is low, increases hourly, and gradually the lungs dilate more fully. Complete expansion is not attained until on the second to the fourth postpartum day (Willi 1948). The deficiency of the respiratory process is apparent to an even greater degree in the premature newborn. Hess and Lundein (1941) describe its respiration as follows: "One of the most

conspicuous features of the premature and of the congenitally weak infant is the poor respiratory effort. In response to the need for oxygen the premature infant inspires at birth, but its muscular power is weak and its efforts are insufficient to raise the thoracic wall and thus expand the pulmonic cavity. As a result, though the large bronchi are filled with air, many of the small bronchioles are not dilated and a large portion of the lung remains in a fetal state and may require even weeks for its complete expansion."

Since deficiencies thus are encountered in the respiratory process of the premature infant even in the normal state it is apparent that they are all the more manifest in pathological conditions.

According to Ylppö (1919) the respiratory movements of the premature infant frequently are very irregular and superficial, and the entire rhythm uneven. A few deeper inspirations often occur suddenly and then slowly subside, so that actually we have before us a relatively pure Cheyne-Stokes type of respiration. Frequently it is superficial to such an extent that at first glance no movement is detectable. Parrot has depicted this condition with the words: "Leben ohne Respiration."

Ylppö (1931) also describes the attacks of suffocation, or asphyctic attacks, encountered with premature infants, in the following terms: "Die asphyktischen Anfälle sind etwas besonders charakteristisches für die Frühgeborenen. Eine kleinere Frühgeburt, die vielleicht zunächst ganz gut geatmet hat, hört plötzlich damit auf, wird tiefblau, der Puls schlägt zunächst noch ganz gut; bei längerer Dauer kann die Hautfarbe allmählich dunkelgrauschwarz werden. Der Puls wird anfangs frequenter, gleichzeitig aber immer schwächer. Die Kinder können sich aus diesem Zustand spontan erholen; in der Regel braucht man jedoch hier noch ein besonderes Eingreifen seitens des Pflegepersonals oder des Arztes. Die Anfälle treten bei manchen Frühgeburten wiederholt auf. . . . Oft sehen wir sie nur in den ersten Lebenstagen; bei kleinen Frühgeburten können aber ausnahmsweise auch noch

in der 2—3 Lebenswoche bei scheinbaren Wohlbefinden sich asphyktische Anfälle einstellen."

Dédek (1913), Eckstein and Rominger (1921), Salmi and Vuori (1930) as well as other investigators have described the periodic respiration which is encountered in premature infants and which is regarded by e.g. the last two authors as physiological for these infants in their first weeks of life.

Peiper (1930, 1931), who has carried out comprehensive studies on the respiratory process of premature infants, has described in detail different types of respiration encountered, such as for instance ordinary, periodic, gasping (Schnappatmung), etc. According to this investigator the highest type of respiration found in premature infants is a regular breathing resembling that of the adult but mainly abdominal in location and of a higher frequency. He emphasizes in particular the often encountered increase in frequency as the infant fails in strength. Peiper regards periodic breathing (Cheyne-Stokes respiration) as a lower form of respiration, stating: "Diese besteht aus Perioden von langsam an- und abschwellenden Atemzügen, wobei die einzelnen Perioden durch Pausen voneinander getrennt sind." A respiration of even simpler form would be gasping breath (Schnappatmung), which consists of "einzelnen besonders tiefen Atemzügen, die mit einer Öffnung des Mundes, einem zurückziehen der Zunge und einem zurückwerfen des Kopfes verbunden sind. Die einzelnen Atemzüge werden durch lange Atemstillstände bis zur Dauer von mehreren Minuten voneinander getrennt. Die Schnappatmung tritt anfallsweise auf; . . . Die Anfälle von Schnappatmung werden meistens als 'asphyktische Anfälle' bezeichnet."

A number of different theories have been advanced in an effort to explain the respiratory disorders of premature infants. According to the earlier concept these disorders were a manifestation of congenital vital debility, "Lebensschwäche". As typical for the opinion still prevailing in the early years of the present century may be cited the following statement: "Die Organe der gesunden Frühgebarten befinden sich in einem Zustande der Unreife; ihre Funktionen sind zunächst verlangsamt und quantitativ herabgesetzt" (Rommel 1906).

According to Ylppö asphyctic attacks are most frequently attributable to a cerebral trauma, which in extrauterine life may lead to meningeal edema and hemorrhage; these in turn give rise to the attacks. As other causes Ylppö mentions congenital organic diseases of the heart, anomalies of the blood vessels, pulmonary affections of various kinds such as bronchopneumonias, pulmonary hemorrhages, and atelectases. Contributory to the occurrence of respiratory disorders might also be congenital malformations or defects in development, as for instance esophago-tracheal fistula, or hernia of the diaphragm. Among numerous other theories for the cause of respiratory disorders may be mentioned weakness of the peripheral respiratory muscles (Salmi 1932), deficiency of oxygen in the respiratory center due to the sparse blood vessel system of the medulla oblongata (Mali and Räihä 1935), excessive acidity of the blood, which is believed to lower the excitability of the respiratory center (Ylppö), high hemoglobin content of the blood (Räihä and Salmi 1934), chlorine deficiency in the blood (Seckel 1934), pressure on the cervical part of the spinal cord (Föderl 1930), immaturity of the respiratory center (Peiper), occlusion of the respiratory passages by too early inspiration (Moncrief 1935), vernix membranes (Ahvenainen 1948), and errors in the care of the infant, particularly loss of body heat (Hoffman 1938). Smith holds the opinion that the respiratory disorders may arise from injury caused to the mechanism of the respiratory center by prolonged anoxia produced for instance by administration of narcotics to the mother or by a difficult delivery.

As distinct from the true asphyctic attacks and other respiratory disorders of the newborn should be differentiated the *asphyxia* which occurs intrauterinely or immediately *post partum*. This condition is defined by Åkerrén (1947) as follows: "In usual medical terminology asphyxia is employed to designate a condition of suffocation encountered in the fetus *sub partu* or in the newborn and associated with more or less marked hypoxia of the blood and tissues. In the newborn infant asphyxia manifests

practically always as an absence, of shorter or longer duration, of normal and effective respiratory movements." The onset may take place at the intrauterine stage, the principal symptom then being a marked increase or decrease in the frequency of the fetal cardiac sounds. Intrauterine asphyxia, which is mainly produced by derangement of the oxygen content in the placental blood or by obstruction of the blood circulation, for instance upon premature placental separation or compression of the umbilical cord, may directly continue as extrauterine. The regular respiratory movements will then be absent whereas the heart will continue to function. The skin changes in hue, and differentiation thus is made between asphyxia livida (or blue asphyxia), and asphyxia pallida (or white asphyxia). In the former case the child is said to be slightly asphyxiated, the skin is cyanosed, the heart functions fairly well. In asphyxia pallida the child is deeply asphyxiated, with pallid skin, weak action of the heart and greatly depressed muscular tonus. If any respiratory movements are present they are but superficial and irregular breaths. Extrauterine asphyxia may also be produced by, in addition to the same causes which lead to intrauterine asphyxia, derangement in the regulation of the respiratory function by the central nervous system, sometimes associated also with intracranial injury and, in the case of the premature infant, with a condition of debility *per se* (Akerrén). The administration of narcotics to the mother during parturition increases the child's tendency to asphyxia; this particularly is the case in premature births (Lund 1941). Depending upon the degree of severity of the asphyxia, death may ensue either directly or following a transient recovery, or the symptoms may sooner or later disappear. A factor of importance in these circumstances is the presence or absence of serious injuries associated with asphyxia, such as for instance large cerebral hemorrhages or possible injury to the ganglion cells of vital nerve centers produced by prolonged anoxemia (Clifford 1940, Akerrén).

### EFFECT OF BIRTH TRAUMATA ON RESPIRATORY DISORDERS OF THE NEWBORN

The marked significance of intracranial hemorrhage both as a cause of infant death and as a producer of a variety functional disturbances of the brain is a recognized fact. Kehrer uses a descriptive expression: "Ein beträchtlicher Teil der Kinder mit intracranien Blutungen wird nicht lebend sondern sterbend geboren." Günther (1927) states regarding birth traumata that, there is in general no normal delivery without injury to the tissue, and Heidler (1936) speaks as follows of the effect of cranial trauma upon the premature infant: "Diese unreifen Früchte mit ihren weichen Köpfen mit ihren mangelhaft entwickelten Gefäßen sind oft dem Trauma der Geburt nicht gewachsen; sie erliegen den mechanischen Noxen *sub partu* und haben dann gar nicht Gelegenheit an Lebensschwäche zu sterben."

At delivery the head of the fetus is subjected to varying degrees of pressure, and as the connective tissue of the blood vessels of the premature infant is weakly developed, vascular ruptures may readily occur (Ylppö). According to this investigator also the soft consistency of the brain of the premature infant promotes the occurrence of hemorrhages, as the dilating veins obtain no countersupport from the environment. These features are further aggravated by the feeble heart action of the premature child and by the conditions of stasis peculiar to its first days of life, which promote bleeding and enlarge the hemorrhages produced by rupture of the blood vessels.

In evaluating the importance of cerebral hemorrhages as a cause of newborn deaths a number of investigators have attached particular importance to hemorrhages encountered in the region of the medulla oblongata. So Seitz indicates that infratentorial hemorrhages are particularly dangerous to the newborn infant, as they may exert pressure upon the medulla oblongata and the respiratory center. Ylppö found serious respiratory disorders especially in those premature infants who showed heavy edema or large hemorrhages around the medulla oblongata. Esch deals

with the effect of traumatic hemorrhages upon the vital functions and stresses in particular the significance of hematomata in the vicinity of the cerebellum. Meyer and Nassau (1930) state that "selbst geringfügige Blutungen in die Medulla oblongata können zum Tode führen", and Bernhart (1935) writes: "Wohin es in Schädel blütet, ist im allgemeinen gleichgültig, wenn auch Druck auf die Medulla oblongata besonders gefährlich ist."

Schwartz (1927), who carried out comprehensive pathologic investigations on the occurrence of intracranial hemorrhages in still-born infants and in children dying within the first 5 months of life, encountered, in addition to macroscopic intracranial hemorrhages in about two-thirds of the cases, also microscopic intracerebral hemorrhages in most cases in various parts of the brain. These injuries to the central nervous system originating in birth traumata are regarded by Schwartz as the most general cause of respiratory disturbances in the newborn infant. He also encountered hemorrhages in the medulla oblongata in many cases. Indeed, according to him, medullary hemorrhages are to be regarded as the direct cause of numerous newborn infant deaths.

Schwartz (1926) furthermore places special emphasis on the so-called "Minderdruckwirkung" as a factor contributive to intracerebral hemorrhages. After rupture of the bag of waters at delivery, the presenting part of the fetus is subjected to atmospheric pressure whereas its other parts remain under the considerably greater pressure of parturition. Suction of blood into the presenting part therefore takes place, with consequent venous congestion. As a result of this hypotensive pressure action, hemorrhages occur particularly in regions where the drainage of venous blood is carried out by the vena magna Galleni system. According to Schwartz the medulla oblongata is also situated in this region.

In studying the effect of birth traumata upon respiratory disorders attention becomes focused chiefly upon those areas of the brain which regulate the process of respiration and specifically upon the region of the medulla oblongata, which is recognized as occupying a central position in the respiratory mechanism. In connection with respiratory disorders it should be possible to indicate pathologic changes and in particular hemorrhages in

these areas of the brain. However, the fact should be borne in mind that the pathologic changes produced by birth traumata may be extremely minute and very difficult to demonstrate, and infants dying in the presence of typical cerebral symptoms may therefore show an almost negative finding at cranial dissection (Rydberg 1928, Heidler) and even microscopic alterations may be identifiable with difficulty (Hausbrandt and Meier). Ahlström (1942), for instance, states that the cause of immediate post-partum death cannot always be diagnosed, due partly to the fact that "die Todesursache hier oft jenseits des morphologisch Fassbaren liegt".

In respect to the anatomic structure of the brain it has been demonstrated that the cerebellum is composed of firmer tissue than the cerebrum, and that the medulla oblongata is of a still firmer consistency than the cerebellum (Broman 1934). The conditions in the medulla oblongata are therefore less favorable for the occurrence of large hemorrhages, as the surrounding firm tissue offers a support to the walls of the blood vessels. It also would seem probable that the sheltered position of the medulla oblongata (Sänger 1924) and its mobility (Broman) in some manner protect it from the effects of birth traumata, as would be necessary already in view of the vital importance of the medulla.

#### EARLIER INVESTIGATIONS ON MICROSCOPIC HEMORRHAGES OF THE MEDULLA OBLONGATA AND THE PONS IN PREMATURE INFANTS

As mentioned above, attention has been attached already since the time of Seitz to macroscopic hemorrhages in the region of the medulla oblongata in newborn infants. Ylppö has stressed the significance of medulla oblongata hemorrhages in particular in the etiology of respiratory disorders in the premature infant. On the other hand, the number of microscopic examinations for

hemorrhage in the medulla oblongata in association with respiratory disorders in premature infants has remained astonishingly small.

The first histological studies on hemorrhages encountered in the area of the respiratory center were carried out by Lumsden (1923) for the purpose of studying various types of respiratory disorders. This investigator, in experiments on cats, observed various types of respiration depending on the level at which the injury to the medulla oblongata or to the pons was located. He states: "The theory generally held is that the automatic respiratory centre is in the lower part of the bulb and that the regulation of impulses sent out by it is determined by impulses passing to it." He further states on the basis of his investigations as follows, as cited by Dollinger: "Wird bei Hirnblutungen der normale Atemtyp beibehalten, so liegt keine ernstliche Schädigung des Gehirnstamms vor. Wird die Atmung apnoisch, dann besteht eine Blutung in der Brücke. Ist sie nur erschwert und findet sich Spasmus bei der Expiration, so ist die Schädigung auf der Höhe der Striae zu suchen. Fehlt der expiratorische Spasmus bei erschwerter Atmung so liegt die Hemorrhagie in der Spitze des Calamus scriptorius dicht bei 'Noeud vital' . . ."

Kirkwood and Myers (1923), assisted by Lumsden, published a case in which a normally delivered child, two days old, suffered from attacks of cessations of respiration, which after a number of recurrences brought about death within twelve hours. Macroscopic examination at autopsy revealed no findings out of the ordinary but in the microscopic examination of sections small hemorrhages were discovered in the lower part of the pons.

Peiper is of the opinion that there does not exist sufficient justification to warrant the application of Lumsden's results, obtained chiefly in animal experimentation, to newborn infants. He also expressed doubt regarding the statement that a given type of respiration is tied to given organic changes in the respiratory center, for constant alternation of various types of respiration may take place in the same infant.

Schwartz made the observation that hemorrhages in the medulla oblongata were very general in the stillborn and in infants

dying within the first postpartum days, including both premature and fullterm infants. On the other hand, traumata in the medulla oblongata were rare in infants who had survived for a longer time after birth. The hemorrhages encountered in the medulla oblongata tissue had their origin in the capillary tubes or in the small veins. They were situated in different parts of the oblongata but were most frequently found in the environment of the fourth ventricle. In addition to those only microscopically discernible in the tissue of the medulla oblongata Schwartz found in the fourth ventricle hemorrhages which originated in the choroid plexus; some of these even were macroscopically visible. In premature infants these hemorrhages sometimes completely occluded the fourth ventricle. He also reports minute hemorrhages encountered by him in the tissue of the pons.

Larini (1926) reports the case of a child delivered by Cesarean section whose respiration from the tenth day to death on the twentieth day was difficult and gasping. He associated with this respiratory disorder a hemorrhage revealed in the histological examination, which was located in the oblongata in the region of the vagus nuclei.

Creutzfeld and Peiper (1932) describe pathologic examinations of the brain of seven premature infants who had suffered from respiratory disorders. In six cases no hemorrhage was encountered in the region of the brain stem. In one case, in which death had occurred two days *post partum*, the examination revealed, apart from small isolated effusions of blood in the brain stem, hemorrhage from the terminal vein in the cerebrum. The conclusion is drawn by these investigators that fatal respiratory disturbances in the premature child do not originate in intracranial hemorrhage but that death is a result of the immaturity of the central nervous system and of the consequent weakness of the respiratory center. However, the material used in their study only contained three premature infants dying during the first week of life, i.e. within seven hours, sixteen hours, and two days after birth respectively, the ages of the remaining four premature infants ranging from nine to twenty-one days. The report furthermore imparts no information in any of the cases on the course

of gestation and delivery nor on the physical condition of the child prior to hospitalization. As demonstrated by Schwartz in his investigations, hemorrhages in the medulla oblongata are generally encountered only in stillborn infants or those dying within the first three days of life, and the single hemorrhage found by Creutzfeld and Peiper belongs to the latter category. In this child and in three of the four premature infants in the age group of 9 to 21 days Peiper diagnosed pneumonia, which in itself could be regarded as sufficient cause for respiratory disorders in a premature child. Consequently the investigations described cannot in respect to either the nature or the size of the material be regarded as supplying conclusive evidence of the absence of hemorrhages in the medulla oblongata in cases of respiratory disorders in premature infants.

Salmi (1932), who carried out experiments on respiratory disturbances with premature rabbits, also performed some tests in which hemorrhages were produced in the brain and the medulla by artificial traumata. Changes in the type of respiration became manifest in such test animals.

In his study on cerebral hemorrhages in 47 premature and 28 fullterm infants Rydberg (1932) examined sections taken also from the region of the medulla oblongata but found in the medullary tissues no macroscopic hemorrhages and but a few isolated microscopic hemorrhages of no demonstrable importance. The findings made in the medulla oblongata and the pons are not described in the report in greater detail.

The American investigators Hemsah and Canavan (1932) published a study of 53 infants, including 12 liveborn and 6 stillborn premature cases. An examination in each case of one or two sections cut from the medulla oblongata for the purpose of determining the presence of hemorrhages disclosed microscopic hemorrhages in 64 per cent of the cases. In 12 cases a hemorrhage in the medulla oblongata was the only finding supplying evidence on which the cause of death could be diagnosed.

Hausbrandt and Meier, in the histological examination of the spinal cord of 103 fullterm and premature infants, reported hemorrhages in 30 per cent of the cases, mostly in the cervical part of

the cord. Some of the hemorrhages were located in the marginal zone of the cervical part and the medulla oblongata. These investigators place great importance upon the findings and consider microscopic examination of the medulla oblongata and the cervical part of the spinal cord essential in seeking the cause of death of the newborn. Emphasis is also placed by several other investigators upon the microscopic examination of the medulla oblongata of the newborn when inquiry is made into the cause of death (Heidler, Föderl, et al.).

The respiratory center, the principal part of which is considered to be located in the medulla oblongata, forms an extensive area which so far has not been definitely determined but is believed to extend from the margin of the cervical end of the spinal cord through the medulla oblongata and the pons up to the inferior quadrigeminal bodies (Lundsgaard 1937). According to the literature available to the present writer, studies on microscopic hemorrhages of the premature infant occurring in the area of the respiratory center not only are few in number but also report variable results. Great variance of opinion also exists concerning the incidence and significance of these hemorrhages. The work described in the following pages has therefore been undertaken in an effort to shed further light upon this subject and to obtain answers to the following questions:

- 1) *Are microscopic hemorrhages of the medulla oblongata or the pons encountered in premature infants dying immediately after birth or within the first month of life?*
- 2) *Supposing hemorrhages of this kind do occur, are they of importance as an etiologic factor in respiratory disorders in premature infants during the first month of life?*

Before I proceed to describe the actual work of investigation and to present the results obtained, a brief description will be given of the structure and activity of the respiratory center in such extent as is deemed necessary for the treatment of the subject of this study.

## II

### STRUCTURE AND ACTIVITY OF THE RESPIRATORY CENTER

Numerous muscles of different kinds are brought into action in the respiratory movement, such as the intercostal, abdominal, nasal, laryngeal, tracheal and bronchial muscles and the diaphragm. It has been assumed that in addition to the nerve nuclei and the centers of the individual respiratory muscles, situated at different levels in the medulla oblongata and the spinal cord, there exists a superior center which, acting as the focus of respiratory control, has charge of the co-ordination of the various respiratory muscles. The rhythm of contraction of the respiratory muscles is so regulated that the total ventilation is capable of maintaining the gas in the pulmonary alveoli at a practically constant level (Lundsgaard, Schoen 1942, Evans 1945, et al.). It has been demonstrated by transection experiments on animals that the respiratory center, or at least the chief respiratory center, is located in the medulla oblongata (Lundsgaard).

The location of the respiratory center was assumed already by Legallois (1811) and Flourens (1842) to be in the medulla at the point of the calamus scriptorius. In the latter part of the nineteenth century opinions were voiced to the effect that a number of variously situated respiratory centers would exist. So for instance Marckwald (1887, 1890) indicated a center which rhythmically inhibits the medullary respiratory center and is located in the brain stem above the medulla in the region of the inferior colliculus. Lumsden found such a center in the upper part of the pons, designating it as the pneumotaxic center. He

furthermore indicated among others an apneustic center at the level of the *striæ acousticæ* and a gasping center below these *striæ*.

Foerster (1936) states: "Die Atmung beruht auf dem wechselnden Spiel der Inspiratoren und Expiratoren. Dieses wird beherrscht durch das im Hirnstamm, in der Oblongata, der Brücke und der Vierhügelgegend gelegene Atemzentrum."

According to Lundsgaard the respiratory center is not definitely defined as to anatomic limits, in other words no distinctly circumscribed collection of ganglion cells can be indicated in the medulla oblongata which could be stated to constitute the respiratory center. It is to be sought for in the immediate proximity of the nuclei of the ninth to twelfth cranial nerves, and it seems to be fairly large in extent. "We actually may have to speak of a series of respiratory centers situated in an area of the brain stem bounded inferiorly by the lowest point of the *calamus scriptorius* and with the superior boundary located midway in the mesencephalon."

According to Regelsberger (1931) certain organs situated in the mesencephalon influence the finer regulation of respiration, i.e. the depth and rate of breathing, whereas "der Einfluss der höheren Hirnteile des Thalamus und Striatum, ebenso wie der des Grosshirns ist gering."

Schoen points out that so far it has not been solved whether one should presume the existence of one definite respiratory center or of a system of different centers united under a superior governing center. From the point of biological evolution he would regard the latter hypothesis as the more probable.

Ranson (1947) indicates the reticular formation as the location of the respiratory center and defines the latter as extending from a point slightly below the pons to the level of the *calamus scriptorius*. Transection of the brain stem at a point inferior to the latter level will effect an interruption of respiration. By means of electrical stimulation tests on cats and monkeys it has been possible to indicate the extent of the respiratory center and

to demonstrate that this center consists of an inspiratory division located in the ventral part of the reticular formation and an expiratory division located in the dorsal part (Fig. I and II).

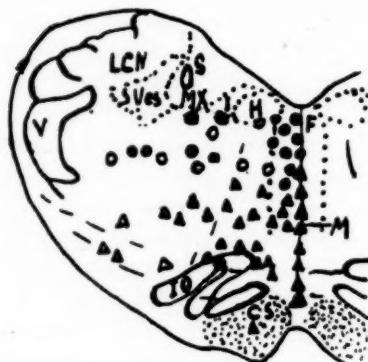


Fig. I

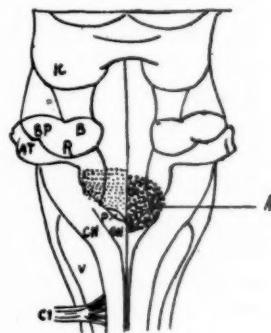


Fig. II

Fig. I.—Section of the medulla oblongata of the cat showing the location of the respiratory center and its separation into a ventrally situated inspiratory subdivision, marked by triangles, and a dorsally situated expiratory subdivision, marked by circles. (After Pitts, Magoun and Ranson.) Corticospinal tract, CS; medial longitudinal fasciculus, F; hypoglossal nucleus, H; intercalate nucleus, I; inferior olive, IO; lateral cuneate nucleus, LCN; medial lemniscus, MX; motor nucleus of vagus, M; tractus solitarius, SVes; spinal tract of the trigeminal nerve, V.

Fig. II.—Dorsal view of the lower brain stem of the cat with the cerebellum removed. Location of the respiratory center as projected on the floor of the fourth ventricle. To avoid overlapping, the expiratory subdivision is indicated only on the right (heavy stippling), the inspiratory only on the left (light stippling). (After Pitts, Magoun and Ranson.) Line A indicates the level of the section shown in Fig I. Acoustic tubercle, AT; brachium conjunctivum, B; brachium pontis, BP; first cervical dorsal root, C1; cuneate nucleus, CN; gracile nucleus, GN; inferior colliculus, IC; area postrema, P; restiform body, R; tuberculum cinereum, V.

According to Evans, the inspiratory center is to be found in the ventral part of the reticular formation, immediately over the

cephalic four-fifths of the inferior olive, and the expiratory center slightly cephalic and dorsal to the inspiratory center. Krieg (1942) has described similarly the location of the respiratory center. Nash (1945) states: "The medullary center of respiration is bilateral and each half is believed to be able to control respiration movements on both sides of the body. There seems to be a still higher 'center' in the pons having some relation to control of breathing, but little is known about it."

In normal circumstances the carbon dioxide tension provides the stimulation of the respiratory center. It is possible that changes in the absolute reaction in the tissue of the respiratory center also contribute. The chemical stimulus of the respiratory center initiates the first inspiration after birth (Rein 1936). In intrauterine life the maternal respiration controls the chemical conditions in the fetal blood through the placental blood circulation. Whenever the regeneration of the placental blood through the blood vessels of the umbilical cord is interrupted, there is a rise in the carbon dioxide content of the fetal blood, and when the threshold is passed the first respiratory movement in the child is created. It is therefore comprehensible that any premature interruption in the placental blood circulation, such as for instance premature separation of the placenta or compression of the umbilical cord, induces a respiratory movement even if the head is not yet expelled. This may cause e.g. aspiration of the amniotic fluid (Rein, et al.). Numerous investigations have been carried out in the past decades to ascertain whether in normal conditions the respiratory movement is recognizable already *in utero*. According to the present conception (Smith, Koller 1948, et al.) isolated breaths indeed occur in the latter part of fetal life but no actual deep respiratory movements take place.

Essential factors in the regulation of respiration are the afferent impulses produced by the alternate expansion and contraction of the lungs and carried to the respiratory center by the vagus nerves. The impulses produced by the expansion of the lungs terminate the inspiration, whereas those evoked by the contraction incite it (Rein, Ranson, et al.). If both vagus nerves

are severed, respiration will become deep and slow. A similar type of respiration is produced if the pons is transected at its superior part. To explain this it has been assumed that the pneumotaxic center is situated in the superior part of the pons or in the mesencephalon, and that in similarity to the vagi it is capable of exerting a restrictive influence upon inspiration and of allowing expiration to begin. Should either of these restrictive mechanisms be absent, respiration will continue but it will be deep and slow, and should both mechanisms be removed the thorax will be held in a fixed state of inspiration interrupted only by the death of the animal (Ranson).

Impulses of stimuli are carried from the respiratory center by way of the anterior funiculi and the anterior part of the lateral funiculi to the nerve nuclei of the respiratory muscles located in the anterior horn of the thoracic and cervical regions of the spinal cord. The principal area of innervation of the inspiratory musculature consists of the region where the phrenic nerve passes out from the cervical part of the spinal cord, in particular the fourth cervical segment, from where the impulses are conducted to the diaphragm, and of the region throughout the thoracic part of the cord where the intercostal nerves pass out. To correspond, the respiratory center is connected with the nuclei of those cranial nerves which innervate the muscles participating in the respiratory effort (Lundsgaard, Ranson, et al.).

Mutual reciprocity is also maintained by respiration and blood circulation in that an increase in the blood pressure will induce inhibition and a decrease excitation of the respiration. Similarly, the activity of the respiratory center is stimulated when there is a decrease in the amount of oxygen and an increase in the carbon dioxide and hydrogen ion concentrations in the blood. These reflex actions go by way of the carotid body, which is located in the wall of the carotid sinus at the bifurcation of the carotid artery and to which a branch is sent out by the glossopharyngeal nerve, and by way of the aortic body in the arch of the aorta, which is in contact through a branch of the vagus nerve with the centers of blood circulation and respiration in the medulla oblongata (Rein, Ranson, et al.).

The reflex actions last described are of importance during asphyxia, as the receptors located in the carotid sinus and the aortic arch may carry stimulatory impulses to the respiratory center even when the latter no longer possesses sufficient irritability by the blood stream in the capillary area (Ranson, Smith).

Peiper has studied the structure of the human respiratory center through observation of the newborn and particularly of the premature newborn. He states: "Das Atemzentrum des Menschen bildet eine physiologische, keine anatomische Einheit. Es setzt sich aus mehreren, physiologisch voneinander abgrenzbaren Bestandteilen zusammen, die sich entwicklung- und stammesgeschichtlich in der Weise gebildet haben, dass die älteren den jüngeren untergeordnet sind und durch deren Tätigkeit gehemmt werden. Bei Frühgeburten zerfällt das unreife Atemzentrum leicht in seine Bestandteile, indem die jüngeren Teile vorübergehend aussetzen, so dass die älteren Teile enthemmt werden. So entsteht eine Notatmung, die nur von den älteren Bestandteilen gesteuert wird." If the activity of the respiratory center is disturbed in such a manner that two subcenters function simultaneously, various intermediate types of respiration are encountered in the premature infant. In conformity with this theory Peiper is of the opinion that the respiratory disturbances which menace the life of the premature infant arise "auf die Unreife und den Zerfall ihres Atemzentrums". However, the question is left open as to what factors play the principal role in the breaking up (Zerfall) of the respiratory center, i.e. in the causation of the respiratory disturbances.

It may also be mentioned that Douglas and Haldane (1909) have demonstrated that periodic respiration can be experimentally induced in any human being by the following procedure.

The subject, comfortably seated, breathes deeply and rapidly for about two minutes. This is followed by a pause of about the same length. When the respiratory effort is resumed, breathing is periodic for a while. These investigators offer the following explanation of this experiment. During the primary interruption of respiration the alveolar oxygen pressure decreases; simultaneously the oxygen pressure in the arterial blood and in the respiration centers also decreases, leading to accumulation of lactic acid in these centers. Thus a much lower pressure of carbon dioxide is

required to effect stimulation of the respiratory center than in normal conditions. The respiratory movements evoked by the stimulus suddenly increase the oxygen pressure in the alveoli, arterial blood and respiratory centers, due to which the lactic acid disappears from the centers, and the carbon dioxide pressure there present, which under the influence of the respiratory movements has decreased, is not sufficient to reach the threshold of irritability of the centers until a further accumulation of lactic acid has been accomplished during a new interruption of the respiratory effort. A deficiency of oxygen therefore brings about the change in the respiration which makes it periodic in type.

On the basis of the above theory Mali and Räihä state that the primary causative factor in periodic respiration in premature infants is an oxygen deficiency in the respiratory center brought about by a sparse capillary system. It is also unknown to what extent the connections of the central nervous system are capable of faultless operation in premature infants of a very small size, as the anatomic structure of the interconnections between their nerve cells are still in a stage of development (Räihä 1946).

### III

## PERSONAL INVESTIGATIONS

### INVESTIGATION METHODS AND MATERIAL

This study is divided into two parts, viz. clinical observations and pathological examinations.

#### CLINICAL OBSERVATIONS

The following procedure was employed in conducting the observations. When a premature infant or fullterm child with respiratory difficulties or otherwise in a poor condition was born or entered for care at any of the hospitals mentioned in the preface to this report, a telephone message was sent to the author, who immediately arrived at the hospital for observations. As these hospitals are located widely apart in different parts of the city and such a child's life is often of short duration, it was soon found that the original plan of graphically recording every child's respiration could not be followed. It was also observed that the child's type of respiration varied from time to time to such an extent that a graphic presentation restricted to any specific period of time would be of no great value. Further, in order to obtain dependable graphs it would be necessary, according to e.g. Peiper, to perform the recording mainly while the child is asleep, as it often moves about restlessly when awake and the type of respiration therefore undergoes change. For this reason the investigations were limited to observation of the general type and irregularities of the child's respiration, such as cessations, periodic and gasping respiration. Particular attention was also attached to the rate of breathing and to changes in this frequency. The general condition of the child was noted both immediately after birth and later, and note was made of the heart action and of possible cyanosis or pallidity. In the great majority of cases the author had the opportunity of making personal observations

nearly through the entire life of the infant. In a part of the cases — mostly infants dying so soon after birth that the author did not see them alive — the source of the observation material is, in addition to the case report, the observations of the attending physician or the hospital nurse. The cases sent to the Children's Hospital of the University of Helsinki in the years 1946 and 1947 were almost without exception cared for in the oxygen couveuse because of respiratory difficulties, and clinical observation could therefore be carried out with relatively great facility, the author being furthermore at the time the premature infant ward physician. In all the cases observed the course of pregnancy and delivery was also noted from the case reports.

It was the author's purpose to observe chiefly the condition of such premature or fullterm newborn infants who presumably could not survive after birth or who could live for a few days at the most, and attention was principally directed to the presence of respiratory disorders. A small number of infants with respiratory disorders living for a few weeks but not over 30 days as well as children in whom no respiratory disorders were established were also subjected to observation. A few stillborn children are also included. In the total series of cases comprising 74 newborn children there were 51 liveborn and 3 stillborn premature infants and 14 liveborn and 6 stillborn fullterm infants. The term "premature infant" designates in the present work a child weighing at birth 2,500 g. or less. The premature cases in this series include three twin and one triple pregnancy.

#### PATHOLOGICAL EXAMINATIONS

A complete autopsy was performed on each case with the exception of one liveborn premature infant and two stillborn fullterm infants for whom opening of the skull only was approved. The autopsy was generally performed within 24 hours *post mortem*, in most cases within 6 to 12 hours.

The following procedure was employed. An incision was made from one temporal region to the other over the occipital region and the skull was exposed. In the parietal region on either side of the sagittal suture, 1 cm. from the median line, an opening about 2 by 3 cm. in size was made, through which it was possible to see any unclotted blood present on the convexity of the brain under the dura mater. Starting from this opening and proceeding parallel to the sagittal suture the skull was opened up

to the frontal region. The incision was first carried dorsally in the occipital direction, then laterally to the temporal region, and thence anteriorly to the frontal region. The entire convexity of the cerebrum was thus exposed and the falx cerebri and the tentorium cerebelli could be examined at the same time. The falx was then detached from the front, the basal section of the brain was examined, the cranial nerves were severed and the brain was removed intact. The medulla spinalis was severed  $\frac{1}{2}$  cm. inferior to the medulla oblongata. Prior to the latter operation the inferior section of the medulla oblongata and the cervical part of the spinal cord were in many cases exposed by laminectomy. In the majority of cases a lumbar puncture was performed about one hour prior to the autopsy for establishment of possible hemorrhage into the cerebrospinal fluid, and at the same time 8 to 10 cc. of a 10 per cent solution of formalin was injected into the spinal canal to facilitate the performance of the autopsy by rendering a firmer consistency to the brain. With a few exceptions, the autopsies were personally made by the author. In a few cases the technique differed from that described above in so far that the skull was opened along the sutures and the cerebrum was removed separately after transection of the brain stem. The brain and the medulla oblongata were either placed intact in a 10 per cent solution of formalin or the medulla and the pons only were placed in formalin whereas the rest of the brain was immediately sectioned.

The medulla and the pons were cut into slices 3 mm. thick, which were embedded in paraffin, and numerous microscopic sections were made of each slice. In some cases sections were made from the entire area of the slice at intervals of from 150 to 200  $\mu$ . In all cases the highest sections were cut from the medulla at the margin of the pons and the medulla, and the lowest sections at the margin of the medulla and the cervical region of the spinal cord. The pons was examined in all but two of the 74 cases (cases No. 93/46 and 104/46). The sections were in most cases made only from the caudal two-thirds of the pons. On an average a total of about 40 microscopic sections per case were made from the medulla and the pons. In the case of ten premature and two fullterm infants, microscopic sections were also made from the region of the quadrigeminal bodies.

The paraffin sections were stained mainly by the hematoxylin-van Gieson method. Also the hematoxylin-eosin, Weigert-Pal, toluidin blue and Prussian blue techniques were used. Scharlach-R staining for fat was made on frozen sections in a part of the cases. The sections to be stained were mostly 5  $\mu$  in thickness, being in a small part of the series 10  $\mu$  (Weigert-Pal and scharlach-R stainings).

The preparation and staining of the microscopic specimens were carried out in the Department of Pathologic Anatomy in the University of Helsinki.

#### MATERIAL

The series of cases studied in the present investigation consists of 51 liveborn and 3 stillborn premature infants, and 14 liveborn and 6 stillborn fullterm infants. Among the liveborn are included 4 premature and 3 fullterm children born in a state of asphyxia, all of whom showed postpartum signs of life but with whom spontaneous breathing did not start or in whom only a few superficial respiratory movements were seen (child in agonal condition).

The total number of infants examined are classified in Table I according to weight at birth and age at death.

TABLE I  
*Classification of Cases according to Weight at Birth and Age at Death*

Age at Death	Weight at Birth, grams							
	Under 1,000	1,001— 1,500	1,501— 2,000	2,001— 2,500	Total	Premat. Infants	Total over 2,500	Total All Infants
Stillborn .....	1	1	—	1	3	6	9	
Under 2 hours .....	6	5	1	1	13	4	17	
2—24 hours .....	3	4	5	2	14	2	16	
1—3 days .....	2	1	1	2	6	6	12	
4—7 " .....	1	3	4	1	9	—	9	
8—14 " .....	—	—	—	2	2	1	3	
15—30 days .....	—	3	3	1	7	1	8	
Total	13	17	14	10	54	20	74	

The premature infants are divided on the basis of the weight at birth into four groups, at gradations of 500 g. Children under 1,000 g., 13 in all, form a separate group. The 1,001—1,500 g. group is the largest, consisting of 17 cases, that of 1,501—2,000 g. com-

prises 14 cases, and that of 2,001—2,500 g. 10 cases. Infants in the different birth weight categories thus form fairly even groups in the series. No distinction is made in the classification between a premature child (weight at birth 1,250—2,500 g.) and an immature child (600—1,250 g.) (Ylppö 1947), as this point was not considered to be of any significance in dealing with the cases. Immaturity of the respiratory center having been regarded by some authorities (Peiper) as the causative factor of the respiratory disturbances, it was considered advisable to also include in the material children who were at the lowest margin of viability but in whom respiratory effort nevertheless was observed. The group of premature infants under 1,000 g. therefore includes two children (twins) weighing less than 600 g. at birth, i.e. 570 g. and 500 g.

The fullterm infants, i.e. children weighing over 2,500 g., form one series of 20 cases, which is not subdivided according to weight at birth.

In the series of 51 liveborn premature infants, 13 (25 per cent)<sup>1)</sup> lived less than two hours, 27 (53 per cent) died within the first 24 hours, 33 (65 per cent) within the first three days, and 42 (82 per cent) during the first week of life. Two (4 per cent) of the total number of liveborn premature infants died during the second week and 7 (14 per cent) between the fifteenth to thirtieth day after birth.

In the series of 14 liveborn fullterm children, 4 (28 per cent) died within two hours, 6 (43 per cent) within the first 24 hours, 12 (86 per cent) within the first three days, and 12 (86 per cent) within the first week of life. One of the remaining two infants died during the second week and one between the fifteenth to thirtieth day (on sixteenth day).

It is therefore seen that about one-fourth of all the liveborn children, both premature and fullterm, died within the first two

<sup>1)</sup> To facilitate comparison, the results obtained are expressed in percentages in addition to number of cases although the author is fully aware of the inaccuracy of the percentages as such in view of the smallness of the material involved.

hours *post partum*, about one-half within the first 24 hours, and a full four-fifths within the first week of life. As a comparison may be mentioned that for instance calculations made on Brander's material show that 65 per cent of the premature infants living at the most one month died within 24 hours and 87 per cent within five days after birth.

Table II indicates the presentation of the children at birth, their condition after delivery and the number of deliveries in which operative intervention was necessary.

TABLE II  
*Presentation at Birth, Postnatal Condition, and Number of Operative Cases*

Presentation	P r e m a t u r e		F u l l t e r m	
	Liveborn	Stillborn	Liveborn	Stillborn
Vertex .....	29	2	12	3
Breech .....	17	1	—	1
Oblique .....	—	—	—	2
Brow .....	—	—	1	—
Face .....	—	—	1	—
Cesarean section ...	2	—	—	—
Not stated .....	3	—	—	—
Total	51	3	14	6

Postpartum Condition	P r e m a t u r e		F u l l t e r m	
	Total	Operative	Total	Operative
Lively .....	41	5	8	—
Slightly asphyxiated .	3	1	2	1
Deeply asphyxiated ..	7	1	4	1
Stillborn .....	3	—	6	3
Total	54	7	20	5

Breech positions were very frequent in this premature infant material, occurring in 18/54 cases<sup>1)</sup> (35 per cent), which is higher than the incidence generally noted. Parviainen (1941) found in a

<sup>1)</sup> Read: 18 out of 54 cases.

series of 4,320 premature births breech presentations in 808 cases, which is equal to 19 per cent, whereas in Sunde's material of 200 infants dying of intracranial hemorrhage, 61 per cent of which comprised premature infants, breech presentations occurred in 42 per cent. It is regarded that in normal conditions 3 per cent of all births occur by breech presentation (Jaschke-Pankow 1923).

With the fullterm infants in the author's series, breech presentation was encountered in one case only out of twenty deliveries. Other presentations found with the fullterm infants were oblique in two cases, brow in one case, and face in one case. None of these presentations were encountered with the premature infants.

The liveborn premature infants were lively in 41/51 cases (80 per cent), whereas they were slightly asphyxiated in 3/51 cases (6 per cent) and deeply asphyxiated in 7/51 cases (14 per cent). Of the liveborn fullterm infants 8/14 cases (57 per cent) were lively, 2/14 cases (14 per cent) slightly asphyxiated and 4/14 cases (29 per cent) deeply asphyxiated. The cases of deep asphyxiation also include the four premature and three fullterm infants born in an agonal condition.

Operative deliveries occurred among premature infants in 7/54 cases (13 per cent) and among fullterm infants in 5/20 cases (25 per cent), the incidence of operative intervention thus being higher in the fullterm deliveries. The operative procedure in premature deliveries consisted of extraction of breech presentation in 3 cases, internal podalic version and extraction in 1 case, forceps delivery in 1 case, and Cesarean section in 2 cases. In fullterm deliveries there was extraction of breech presentation in 2 cases, internal podalic version and extraction in 1 case, forceps delivery in 1 case, and correction of brow presentation in 1 case.

One case each of congenital syphilis and cerebral meningitis were diagnosed in the premature infants. One fullterm child was affected with hydrocephalus and in one there were congenital anomalies in the urogenital organs.

Syphilis was encountered in three and nephropathy in four

mothers giving birth to premature children. Three fullterm parturients were affected with nephropathy and one of these also had syphilis.

In 32 cases premature birth was given by primiparae and in 21 cases by multiparae; in one case the number of earlier deliveries was not known. The mothers of fullterm infants were 6 primiparae, 13 multiparae, and one whose deliveries were unknown in number.

### INTRACRANIAL HEMORRHAGES IN PREMATURE AND FULLTERM INFANTS

#### MACROSCOPIC INTRACRANIAL HEMORRHAGES IN PREMATURE INFANTS

In studying the occurrence and importance of microscopic intracranial hemorrhages attention should also be paid to macroscopically demonstrable hemorrhages. All hemorrhages clearly observable within the cranial cavity at autopsy were in the present work regarded as macroscopic intracranial hemorrhages with the exception of cases in which the only findings were minute effusions of blood between the folds of the falx or the tentorium, in as much as the prevalent conception (Kehrer, Baar, et al.) regards them as physiological in origin and therefore devoid of clinical significance.

Macroscopic intracranial hemorrhages were encountered in the premature infants in 25/54 cases, or in 46 per cent. According to e.g. Kehrer intracranial hemorrhages encountered in newborn infants may be classified into epidural, duraduplicature, leptomeningeal, intracerebral, intraventricular, intracerebellar and basilar hemorrhages. According to this classification the hemorrhages encountered in the present material may be grouped as in Table III.

TABLE III

*Macroscopic Intracranial Hemorrhages in Premature Infants*

Nature of Hemorrhage	Liveborn	Stillborn	Total
Duraduplicature .....	8	—	8
Leptomeningeal .....	14	—	14
Intraventricular .....	2	—	2
Basilar .....	—	1	1
Total	24	1	25

In determining the above grouping of hemorrhages the criterion used was the principal localization of the hemorrhage according to the interpretation made from the autopsy records. In numerous cases there also was a finding of hemorrhage elsewhere in the brain. In one case the duraduplicature hemorrhage originated from a laceration of the falx and in seven cases from a tentorial laceration, which latter was bilateral in three cases. In two cases profuse hemorrhage was encountered in connection with the tentorial laceration. In one of the cases it formed an extensive infratentorial bleeding reaching to the region of the pons and the medulla (case No. 102), and in the other case the hemorrhage was mainly supratentorial, extending to the region of the occipital lobe (case No. 30/47). In connection with the falx laceration an abundance of unclotted blood was present in the cranial cavity. Other duraduplicature hemorrhages were fairly small.

In the majority of cases the leptomeningeal hemorrhages formed large areas of coagulated blood mainly on the convexity of the cerebrum. However, in a few cases the hemorrhage extended also to the cerebellar region and as far as the basal part of the brain. In three cases the hemorrhage formed an extensive mass of coagulum around the medulla oblongata (cases No. 36, 38 and 206), and in two of these cases it blocked the foramen magnum (cases No. 36 and 206). Intraventricular hemorrhage was established as an independent finding in two cases (cases No. 10 and 19), in addition to which effusion of blood into the ventricles was encountered in five cases in connection with a leptomeningeal hemorrhage. As basilar hemorrhage was classified a case (case

No. 9) in which coagula were present in the basal region of the brain of a stillborn child although the point of origin of the hemorrhage could not be determined.

There is reason to note that macroscopic intracranial hemorrhages were encountered in six of the seven premature children delivered by operative intervention.

The incidence of macroscopic intracranial hemorrhages in the premature infants in relation to the weight at birth and the age at the time of death are listed in Table IV.

Further findings at autopsy were pronounced or moderately pronounced edema of the leptomeninges in 35 cases, mild edema in 7 cases, and hyperemia of the leptomeninges or no special notation regarding these membranes in 12 cases.

Prior to autopsy a lumbar puncture was performed on 39 premature infants. In six cases (15 per cent) blood was present in the cerebrospinal fluid.

#### MICROSCOPIC HEMORRHAGES OF THE MEDULLA OBLONGATA AND THE PONS IN PREMATURE INFANTS

As *microscopic hemorrhages of the medulla oblongata* are designated in the present study effusions of blood present either in the medullary tissue, including the leptomeninges, or in the fourth ventricle and clearly demonstrable in microscopic specimens. In addition to serial sections, microscopic specimens were also made in most cases of definitely recognized or suspected cases of hemorrhage from the focus of the hemorrhage by cutting the entire slice into sections at intervals of about 150 to 200  $\mu$  for examination of the hemorrhage and determination of its extent.

Microscopic hemorrhages of the medulla oblongata were encountered in the premature infant series in 20 cases out of 54, or in 37 per cent of all the premature infants in the series. In 10 cases (18 per cent), no findings of macroscopic intracranial hemorrhage were made in addition to the microscopic hemor-

rhage of the medulla oblongata. Macroscopically established intracranial hemorrhages being present in 25 cases, the total number of recognized cases of hemorrhage, i.e. macroscopic intracranial hemorrhages and microscopic hemorrhages in the medulla oblongata alone, was  $25 + 10 = 35$ , equal to 65 per cent of the premature infants examined in the course of this work.

The recognized microscopic hemorrhages of the medulla oblongata in the premature children, grouped according to weight of children at birth and age of death, are listed in Table IV, which also includes as comparison the figures for macroscopic intracranial hemorrhages.

TABLE IV

*Macroscopic Intracranial Hemorrhages and Microscopic Hemorrhages of the Medulla and Pons in Premature Infants, Classified according to Weight at Birth and Age*

Weight at Birth, grams	No. of Cases	Macroscopic Intracranial Hemorrhages	Microscopic Hemorrhages	
			Medulla Oblongata	Pons
Under 1,000 ..	13	6 (46 %)	4 (30 %)	2
1,001—1,500 ..	17	9 (53 %)	7 (41 %)	2
1,501—2,000 ..	14	6 (43 %)	4 (29 %)	2
2,001—2,500 ..	10	4 (40 %)	5 (50 %)	3
Total	54	25 (46 %)	20 (37 %)	9

Age at Death	No. of Cases	Macroscopic Intracranial Hemorrhages	Microscopic Hemorrhages	
			Medulla Oblongata	Pons
Stillborn .....	3	1	1	—
Under 2 hours ..	13	7 (54 %)	3 (23 %)	2
2—24 hours ..	14	8 (57 %)	5 (36 %)	2
1—3 days ..	6	3 (50 %)	5 (83 %)	3
4—7 .. .	9	3 (33 %)	5 (56 %)	2
8—14 .. .	2	—	1	—
15—30 .. .	7	3 (43 %)	—	—
Total	54	25 (46 %)	20 (37 %)	9

The variance seen in the incidence of microscopic hemorrhages of the medulla oblongata in the different weight groups of premature infants is fairly small. Thus no definite difference in the

number of medullary hemorrhages grouped according to the child's weight at birth can be established, at least not in the small number of cases available in each group of the present series. Neither can such variances be noted in the case of the macroscopic intracranial hemorrhages if grouped according to the child's weight, with gradations of 500 g. However, if the latter cases are divided into two groups, i.e. premature infants weighing 1,500 g. or less and those weighing over 1,500 g., it will be found that macroscopic intercranial hemorrhages are encountered more frequently in infants in the first mentioned weight category.

Seen from the point of age, the microscopic hemorrhages of the medulla oblongata were most frequent in infants dying at the age of one to three days, for hemorrhages were encountered in five-sixths of these newborn. Upon closer study of the incidence of microscopic hemorrhages in the different age groups, the results would seem to indicate at first an increase in the incidence as the hours and days pass. More hemorrhages are encountered at the age of two to twenty-four hours than under two hours, and the largest number of hemorrhages were present at the age of one to three days, whereas less hemorrhages were already encountered at four to seven days. After this age a microscopic hemorrhage of the medulla was encountered only once, in a child dying at the age of 8 days. Even if the small number of cases makes it difficult to make definite conclusions also in this respect, notice is drawn to the fact that macroscopic intracranial hemorrhages also were encountered most frequently in children surviving three days at the most, after which the incidence of hemorrhage tended to decline.

In regard to the location of the microscopic hemorrhages of the medulla it is noted that they were most generally encountered in the fourth ventricle (14 cases) either as a sole finding (9 cases) or with a collateral finding of hemorrhage in the medullary tissue (5 cases). In eleven cases the hemorrhage was found in the actual tissue of the medulla, where in some cases it was present in several places. Such hemorrhages occurred mostly in the vicinity of the fourth ventricle or in the region of the inferior olive, in addition to which there was subpial hemorrhage in the

lateral parts of the medulla oblongata in two cases and in the leptomeninges in two cases.

In studying the location of the microscopic hemorrhages of the medulla in the premature infants dying at various ages it is worthy of note that, apart from one stillborn case, hemorrhages were only encountered in the medullary tissue of those infants who lived three days or less. In infants dying on the fourth to seventh day the hemorrhages were all localized in the fourth ventricle, and the same was also true of the only hemorrhage encountered in a child dying on the eighth day.

As already was mentioned above, Schwartz in his studies found hemorrhages of the medullary tissue and the fourth ventricle exclusively in stillborn premature infants or those dying on the first days after birth; the hemorrhages in the actual medullary tissue were only found in infants stillborn or dying within the first three days. The findings made in the investigation on premature infants now reported upon are an indication in the same direction. Detailed data on some of the typical findings of hemorrhage in the medulla oblongata are given below.

All the hemorrhages encountered in the medullary tissue proper were small and had apparently escaped from the capillaries and in some cases from the small veins. In association with a hemorrhage the capillaries were filled with an abundance of blood, and in some cases not only actual hemorrhages were found but also isolated blood cells were seen here and there outside the dilated capillaries. Hemorrhages were present principally in the region of the inferior olive and in the roof, floor or lateral wall of the fourth ventricle.

Case No. 6 is a child weighing at birth 2,020 g. and dying at 25 hours in whom a hemorrhage is seen in the dorsal margin of the hilus region of the olive, around a small blood vessel. The hemorrhage has slightly displaced the surrounding nerve tissue. No cell accumulation around the hemorrhage or decomposition of the blood cells in the hemorrhage can be observed (Illustration No. 1). Near by, also in the region of the hilus, is a second hemorrhage which is similar but slightly smaller. In the upper part of the medulla of the same child, near the floor of the fourth ventricle, dorsal to the hypoglossal nucleus, hemorrhages are seen

around the small blood vessels but without recognizable reaction in the surrounding tissue (Ill. No. 3 a and 3 b).

**Case No. 102**, weight at birth 2,160 g., age 24 hrs. Pronounced stasis was present. Around a capillary in the dorsal margin of the olive is a small, distinctly circumscribed hemorrhage, which slightly displaces the surrounding tissue (Ill. No. 2). The same child shows blood cells outside a small blood vessel midway in the pons, on its lateral margin. In the region of the medulla and the pons single blood cells are encountered here and there outside the capillaries.

**Case No. 203**, weight at birth 1,730 g., age 40 hrs. The capillaries are very full, and blood is present in the fourth ventricle. In the roof of the fourth ventricle there is a small irregularly bounded hemorrhage, in the region of which are seen blood cells sparsely scattered inside the nerve tissue. There are two capillaries in the marginal zone of the hemorrhage. In the upper part of the medulla, slightly lateral to the raphe and dorsal to the olive, extravascular blood cells are encountered. Isolated blood cells are seen here and there outside the dilated capillaries. Midway in the pons there is in the lateral wall of the fourth ventricle around a capillary tube a minute hemorrhage with diffuse boundaries, in which blood cells have entered between the cells and fibers of the nerve tissue (Ill. No. 8). No displacement of the tissue or cell accumulation is observed in the environment.

**Case No. 26**, weight at birth 2,460 g., agonal. Capillaries are very full. In the superior section of the medulla, near the hypoglossal nucleus, a hemorrhage from a ruptured capillary is found in the floor of the fourth ventricle (Ill. No. 4). At the margin of the pons and the medulla, in the lateral wall of the fourth ventricle, blood is found outside the very full small blood vessels.

**Case No. 30**, weight at birth 870 g., age 2 ds. Capillaries are moderately full. Dorsolaterally from the olive are seen two collapsed small blood vessels, outside of which there are some blood cells. Small hemorrhages are found in the lower part of the pons, in the roof of the fourth ventricle.

**Case No. 39**, weight at birth 1,560 g., age 3 hrs. In the inferior lateral part of the medulla, at the level of the calamus scriptorius, is a fairly large hemorrhage beneath the pia (Ill. No. 5). The blood vessels in the leptomeninges are full.

**Case No. 36**, weight at birth 1,080 g., age 29 hrs. Capillaries are fairly full, and there is much blood in the fourth ventricle. In the leptomeninges and externally to them there are extensive hemorrhages in the region of the medulla (Ill. No. 6). In the outer zone of the hemorrhage there are large mononuclear cells as well as cells ingesting fragments of brown pigment (phagocytosis).

**Case No. 206**, weight at birth 780 g., age 24 hrs, 30 min. The capillaries are very full and blood is present in the fourth ventricle (Ill. No. 7). Extravascular blood is encountered in the anterior septum in the region

of the medulla. In the region of the pons, large hemorrhages have occurred in the leptomeninges. Blood cells in the process of decomposition are not found.

In addition to the cases described above, which illustrate hemorrhages of various types present in the medulla oblongata, there were a few in which blood cells were found outside very full leptomeningeal blood vessels, for instance in the vicinity of the anterior septum. However, such findings were not recorded as hemorrhages (with the exception of cases No. 36 and 206), for when the microscopic specimen is being prepared the leptomeninges in the region of the oblongata are liable to break and blood cells from the ruptured pial blood vessels may readily enter the surrounding connective tissue, which is of a loose texture. With the exception of case No. 36, no changes which would have given evidence of intravital origin could be observed in the hemorrhages encountered in the leptomeninges in the region of the medulla.

The hemorrhages in the fourth ventricle were in some cases recognizable already by the naked eye, an actual blood tamponation of the fourth ventricle being present in three cases (cases No. 1, 36 and 206). In the majority of cases the effusion of blood into the fourth ventricle was relatively slight but nevertheless clearly demonstrable in microscopic sections cut at various levels. A hemorrhage of the fourth ventricle may originate in, for instance, the choroid plexus of the ventricle (Schwartz), or a hemorrhage of subependymal location may rupture into the fourth ventricle and thence spread into other ventricles (Mac Gregor). In some cases a basal hematoma external to the fourth ventricle may penetrate into it (Henschen 1913). In my own studies the source of the hemorrhage could not always be determined with certainty. In some cases, again, the hemorrhage apparently had its origin in an excessively full blood vessel network of the choroid plexus, and at least in one case (No. 99/46) in the subependyma. Hemorrhages of the fourth ventricle exhibited uniformity in so far that they only were present either in stillborn infants or in infants surviving but a few days (not

over 8 days). MacGregor, for instance, states that ventricular hemorrhages are rare with infants over one week of age.

In a few cases in which a child showing hemorrhage in the fourth ventricle had lived for some days, blood cells in the process of decomposition were also encountered in the hemorrhagic area (e.g. cases No. 19 and 99/46).

It was found that 8/20 cases (40 per cent) of the premature infants who showed microscopic hemorrhages of the medulla had been born by breech presentation, 11 by vertex presentation, and 1 by Cesarean section. As 35 per cent of the total series of premature cases in this study were breech presentation births, it apparently was of no consequence in the causation of microscopic hemorrhages of the medulla oblongata whether the child was delivered by vertex or by breech presentation.

There were seven operative deliveries in the entire premature infant material, involving a forceps delivery in one case (No. IV), extraction of breech presentation in three cases (No. 102, 36, and 37), internal podalic version and extraction in one case (No. 38), and Cesarean section in two cases (No. 104/46 and 109/46). Hemorrhage was encountered in the medullary tissue or in the fourth ventricle in four of these cases, i.e. in two of the extractions of breech presentation, in the one internal podalic version and extraction, and in one Cesarean section. In the last mentioned case (No. 104/46) the pains had begun already before operation was undertaken. It may be mentioned here that in the other case of Cesarean section, resorted to because of eclampsismus, no hemorrhage was found in the medulla oblongata, whereas rather extensive leptomeningeal hemorrhages were present in the occipital lobe. The above described findings therefore seem to indicate that operative delivery is not of decisive importance in the causation of microscopic hemorrhages of the medulla oblongata, even if such hemorrhages were encountered in these cases slightly more frequently than in the other cases.

Tentorial laceration was found in a total of seven cases in the entire series. In two of them (cases No. 26 and 102) there was a collateral finding of microscopic hemorrhage in the medulla. Consequently a tentorial laceration was not found to have any

correlation with the occurrence of microscopic hemorrhages in the medulla.

Fourteen (34 per cent) of the 41 premature infants who were born in a live condition showed microscopic hemorrhages in the medulla. Ten premature infants were born in a state of asphyxia, and in five of them (50 per cent) there was microscopic medullary hemorrhage. It thus appears probable that the incidence of hemorrhage is higher with the asphyctic newborn than with the live newborn.

Microscopic hemorrhages were found in the medulla oblongata of three of the six premature children whose cerebrospinal fluid was blood-tinted at the lumbar puncture made before autopsy on 39 of these infants.

Twelve (60 per cent) of the mothers whose children showed microscopic hemorrhages of the medulla oblongata were primiparae. As the entire premature infant material contained primiparae in 59 per cent, the number of pregnancies apparently has had no influence on the presence of microscopic hemorrhages of the medulla. In one of the three cases in which the mother of a premature child was syphilitic and in one of the four cases in which she had nephropathy there was a finding of microscopic hemorrhage in the child's medulla. The mother's state of health therefore apparently had no effect in these cases upon the occurrence of medullary hemorrhage in the child. Neither could any correlation be observed between the age of the mother and the presence of microscopic medullary hemorrhages in the child.

Hemsahrt and Canavan found in their studies that primiparity, age of mother, mode of delivery, or child's stage of development were in no etiological relation to the presence of microscopic hemorrhages in the medulla oblongata. The present study points to a similar inference in these respects. However, whereas Hemsahrt and Canavan found medullary hemorrhages in all their cases of maternal syphilis (4 cases) the children of syphilitic mothers in the author's investigation (3 cases) did not show a higher incidence of medullary hemorrhages than other children.

The author has found in the literature no reports on comparative studies of microscopic examinations for possible medullary

hemorrhage in cases where a lumbar puncture on a premature infant had yielded blood-tinted cerebrospinal fluid. As stated above, the specimens of cerebrospinal fluid drained from 39 premature infants contained blood in six cases, and in three of these cases microscopic medullary hemorrhage was also encountered. This would indicate the presence of microscopic hemorrhages of the medulla oblongata in 50 per cent of the cases in which a lumbar puncture gives a finding of blood-tinted cerebrospinal fluid. However, the confirmation of this conclusion would require a study material of considerably greater size.

#### *Microscopic Hemorrhages in the Area of the Respiratory Center*

A comparison of the sites of the hemorrhages encountered in the medullary tissue with, for instance, the diagrammatic drawing of the area of the respiratory center made by Pitts, Magoun and Ranson on the basis of animal experiments (Fig. I) gives reason to assume that the hemorrhages identified in the medulla oblongata may have been localized in six cases within the area of the respiratory center. These cases include the hemorrhages in the dorsal part of the olive (cases No. 6 and 102), dorsal to the olive (cases No. 30 and 203), and in the floor of the fourth ventricle (cases No. 6, 26 and 62). Classified according to this criterion all the other hemorrhages found in the medullary tissue would probably be situated outside the area of the respiratory center (cf. Ill. 15 and Fig. I).

#### *Microscopic Hemorrhages of the Pons in Premature Infants*

Studies on the presence of microscopic hemorrhages in the pons were made in the case of 52 premature infants. In nine cases (17 per cent) there was a finding of hemorrhage in the pons. In eight of these cases microscopic hemorrhages also were present in the region of the medulla oblongata, and in one case only (case No. 65) the sole finding was the hemorrhage encountered in the pons, near the floor of the fourth ventricle, without any collateral finding of a medullary hemorrhage. However, in the last men-

tioned cases there were macroscopic cerebral hemorrhages from tentorial laceration.

All the hemorrhages encountered in the pons, examples of which were given above in connection with medullary hemorrhages, were similar in extent and nature to those in the medulla, being in the majority of cases situated in the vicinity of the fourth ventricle, mainly in the roof and lateral walls. One case only showed subpial hemorrhage in the lateral part of the pons (Ill. 9), and one case leptomeningeal hemorrhage in the same location.

The incidence of hemorrhage in the pons in the different birth weight groups showed no variations of importance. In respect to age it was noted that in seven cases these hemorrhages were present in children at the most three days old, and in two cases in children five days old (Table IV). No changes in the surrounding tissues or disintegration of blood cells within the hemorrhagic area were encountered.

In ten premature infant cases microscopic sections were cut also from the margin of the pons and the mesencephalon and from the region of the inferior quadrigeminal bodies. No hemorrhages in the cerebral tissue were encountered in these cases.

#### MACROSCOPIC INTRACRANIAL HEMORRHAGES IN FULLTERM INFANTS

Macroscopically recognizable intracranial hemorrhages were encountered in the series of twenty fullterm infants in thirteen cases (65 per cent). If the liveborn and the stillborn infants are grouped separately, nine (64 per cent) of fourteen liveborn infants and four (67 per cent) of six stillborn infants showed hemorrhage. The location of the hemorrhages, classified according to the main focus, will be seen in Table V.

TABLE V  
*Macroscopic Intracranial Hemorrhages in Fullterm Infants*

Nature of Hemorrhage	Liveborn	Stillborn	Total
Epidural .....	1	—	1
Duraduplicature .....	3	3	6
Leptomeningeal .....	2	1	3
Intraventricular .....	—	—	—
Intracerebral .....	2	—	2
Basilar .....	1	—	1
Total	9	4	13

An epidural hemorrhage was found at the junction of the cranial cavity and the spinal canal, continuing into the region of the superior cervical vertebrae. The hemorrhage seen the most frequently was a duraduplicature hemorrhage, present in six cases. In two cases it had its origin from a bilateral tentorial laceration (cases No. 23 and 31), in two cases from an extensive laceration of the falx (cases No. 12 and 15), and in one case from bilateral laceration of the tentorium and laceration of the falx (case No. 27). In one infant the hemorrhage had escaped at the margin of the falx from the veins passing from the pia to the superior sagittal sinus. The duraduplicature hemorrhages were in the majority of cases large in extent, either situated subdurally on the convexity of the brain or continuing infratentorially as far as the basal part of the brain. In one of the stillborn infants (case No. 23) a wide hemorrhagic area continued into the region of the medulla oblongata and the foramen magnum was blocked by blood.

A leptomeningeal hemorrhage was present in three cases and was situated partly on the cerebral convexity, from where it extended in one case into the subdural space. In all of these cases hemorrhage was present also in the basal part of the brain. The source could not be definitely determined (cases No. 17 and 104).

Intraventricular hemorrhage did not appear as an individual finding, but in two cases of stillborn infants (cases No. 23 and 31)

blood was present in the ventricles in association with profuse duraduplicature hemorrhage.

There were intracerebral hemorrhages in two cases only. These hemorrhages were small, and were situated in one case near the wall of the left lateral ventricle (case No. 5) and in the other in the internal capsule (case No. 28).

As basilar hemorrhage is regarded a case in which hemorrhage was found in the posterior fossa (case No. 68/47) even if its source had not been made clear at autopsy.

Five of the fullterm children were delivered operatively and in all of these cases there was a postmortem finding of macroscopic cerebral hemorrhage. Among them were four cases of duraduplicature hemorrhage, in which operative intervention had been extraction in two cases (No. 23 and 15) (in one of these hydrocephalus was present and the skull became crushed), internal version and extraction in one case (No. 12), and correction of brow presentation in one case (No. 27). One of the cases of leptomeningeal hemorrhage had been a forceps delivery (No. 104), with the child slightly asphyxiated.

The incidence of macroscopic cerebral hemorrhages in the different age groups is shown in Table VI.

The incidence of macroscopic cerebral hemorrhages was found to be somewhat higher in the series of fullterm infants (65 per cent) than in that of premature infants (46 per cent). However, consideration should be given to the fact that the series of full-term infants is considerably smaller than that of premature infants and that furthermore the number of still births was greater in the fullterm infant material and a notably large percentage of the latter (25 per cent as against 13 per cent of premature infants) were born operatively. The fullterm infants were asphyxiated at birth in 43 per cent and the premature infants in 20 per cent. — It should, however, be mentioned here that certain investigators hold the opinion that intracranial hemorrhages are not more frequent with premature than with fullterm infants (Liebe 1940), and e.g. Potter (1941) finds a higher incidence of intracranial hemorrhages with fullterm than with premature infants. Hausbrandt and Meier state that fullterm infants dying

within the first postpartum hours show more frequent and more severe intracranial birth traumata than premature infants.

**MICROSCOPIC HEMORRHAGES OF THE MEDULLA OBLONGATA  
AND THE PONS IN FULLTERM INFANTS**

In the series of twenty fullterm infants *microscopic hemorrhages of the medulla oblongata* were encountered in ten cases (50 per cent). In four cases (20 per cent of the series) no simultaneous finding of macroscopic cerebral hemorrhage was made. Macroscopically recognizable hemorrhages were present in thirteen cases. We find, by adding together the number of intracranial hemorrhages seen by the naked eye and the microscopic hemorrhages in the medulla oblongata alone, that the total number of hemorrhages in this series is  $13 + 4 = 17$  (in 80 per cent of fullterm children in the series).

The occurrence of microscopic hemorrhages of the medulla oblongata grouped according to the age of the child at death is shown in Table VI, to which are also appended for the sake of comparison the figures on macroscopic intracranial hemorrhage in these children.

TABLE VI

*Macroscopic Intracranial Hemorrhages and Microscopic Hemorrhages of the Medulla and Pons in Fullterm Infants, Classified according to Age of Child*

Age	No. of Cases	Macroscopic Intracranial Hemorrhages	Microscopic Hemorrhages Medulla Oblongata	Pons
Stillborn .....	6 *	4	3	—
Under 2 hours ....	4	3	4	—
2-24 , ....	2	2	1	1
1-3 days .....	6	3	2	2
4-7 " .....	—	—	—	—
8-14 " .....	1	—	—	—
15-30 " .....	1	1	—	—
Total	20	13	10	3

As will be seen from the table, microscopic medullary hemorrhages were only encountered in fullterm infants that either were stillborn or died within the first three postpartum days. They were most frequent in children dying within two hours, being present in all the infants in this age group (4 cases). The series contains only two infants over one week old and there was no microscopic hemorrhage finding in either case, whereas one of the two showed a macroscopic intracranial hemorrhage.

In regard to localization of the microscopic hemorrhages of the medulla oblongata in fullterm infants it is found that in seven cases they were situated in the actual medullary tissue. In four of these cases there also was hemorrhage in the fourth ventricle. In three other cases a hemorrhage in the fourth ventricle was the sole finding. The hemorrhages in the actual medullary tissue were under the floor of the fourth ventricle, in the region of the inferior olive, around the central canal, beneath the pia, and in the leptomeninges.

As to the age of the child, hemorrhage in the medullary tissue was present in a child three days old (1 case), and in all the other cases only in stillborn infants (3 cases) and infants dying within two hours (3 cases). Hemorrhage of the fourth ventricle was similarly only present in a stillborn (1 case) and in infants dying within the first three days (6 cases).

In extent and nature the hemorrhages of the medulla oblongata found in fullterm infants were comparable to those observed in premature infants, except that there were no findings of phagocytosis or of decomposed red blood cells. Illustrations 10, 11 and 12 show hemorrhages in the central canal in the lower part of the medulla oblongata and in the fourth ventricle.

The presentations at birth of the fullterm infants showing microscopic hemorrhage of the medulla oblongata were one each of breech, face, brow and oblique presentation and six vertex presentations. No definite etiological relation between the presentation and the medullary hemorrhage can be drawn from this.

There were five operative deliveries in the series of fullterm infants, as follows: one case each of forceps, correction of brow

presentation, and internal podalic version and extraction, and two extractions, one of the latter being the case of hydrocephalus in which the skull became crushed at delivery (case No. 15). In connection with these operative procedures microscopic hemorrhages of the medulla were encountered in two cases only (case No. 12 of internal podalic version and extraction and case No. 23 of extraction of breech presentation). The circumstance of operative intervention apparently had no decisive influence upon the presence of microscopic hemorrhages in the medulla. This observation is of particular interest, for in all the cases of operative delivery of fullterm children macroscopic intracranial hemorrhages were encountered, some being quite extensive.

Three fullterm infants showed tentorial laceration, which was bilateral in every case. In one case a laceration of the falx also was present. Microscopic hemorrhage was found in the medulla oblongata in all these cases. In two cases where laceration of the falx was the sole finding, hemorrhage was not encountered in the medulla. These findings seem to indicate that microscopic medullary hemorrhages are common with fullterm infants in association with tentorial laceration, at least if the latter is bilateral.

The mothers of the fullterm infants in this series were primiparae in six cases and multiparae in 13 cases; in one case the parity was not known. Microscopic medullary hemorrhage was found in the children of four primiparae and six multiparae. No distinct relation of parity to the occurrence of microscopic hemorrhage of the medulla oblongata can therefore be said to exist. The age of the parturient apparently also was devoid of effect on the occurrence of these hemorrhages.

A lumbar puncture was performed prior to autopsy on twelve fullterm children and blood was found to be present in the cerebrospinal fluid in six cases, in three of which microscopic medullary hemorrhages were encountered.

It may be regarded that in three cases the hemorrhages in fullterm infants were localized in the area of the respiratory center (cf. Fig. I). These three cases were one stillborn child (case No.

2), one child born in an agonal condition (No. 32), and one dying at the age of two days (case No. 4).

#### *Microscopic Hemorrhages of the Pons in Fullterm Infants*

Simultaneously with the medullary hemorrhages there also were *microscopic hemorrhages in the pons* in three cases (Table VI). In two of these cases the hemorrhage was situated in the floor or lateral wall of the fourth ventricle and in one case subpially. They were similar in nature to those present in the medulla oblongata.

Microscopic sections were also made from the region of the quadrigeminal bodies in two cases but the examination revealed no hemorrhages in the cerebral tissue.

#### ON PATHOLOGIC CONDITIONS ARISING FROM HEMORRHAGES IN THE BRAIN TISSUE

##### *General*

If an interference in the blood circulation of the brain tissue caused by a hemorrhage or a thrombus completely deprives a given region of the inflow of blood, a necrotic focus is formed in the region of the injury. With the aid of the living cells within the focus a destruction of brain tissue takes place in the necrosed region and a softening is produced. The products of decomposition of the brain tissue undergoing destruction become further disintegrated through the action of scavenger cells of glial or mesenchymal origin, are transformed into fat droplets, and ultimately pass by way of the perivascular spaces with the lymph stream into the blood (Spielmeyer 1922, Weil 1946, et al.). At the site of the original necrosis there forms either a cavity surrounded by glial tissue or a cicatrice of connective tissue, in which also may be present pigment waste produced in the decomposition of the tissues (Schwartz). The softening may form in the course of a few days. If, on the other hand, the circulation disturbance ex-

tends over a small area only and the circulation of blood is able to continue by means of vascular anastomosis, necrosis of tissue need not necessarily arise. In the region of a hemorrhagic focus, gitter cells of glial and mesodermal origin will be formed and the decomposition of the red blood cells takes place in them (Spielmeyer).

"The red blood cells that overflow into the nervous tissue retain their original form for several days and therefore are a reliable indication of recent hemorrhage. Later they disintegrate, are taken up by phagocytic cells that break down the hemoglobin into its components, protein and pigment or hemosiderin (pigmented compound granular cells). The hemoglobin loses its iron and in this form, hematoidin, may be differentiated from the blue-staining hemosiderin by its crystalline form (platelets of yellow or brownish red color) and by the absence of blue staining with potassium ferrocyanide and hydrochloric acid (prussian blue formation). The hemosiderin appears in granular form first in phagocytic cells. These phagocytic cells break down after the digestive process has been completed and free blood pigment may then be seen in the original hemorrhagic area. Other cells take up this free pigment and carry it to the perivascular spaces in the neighboring region. . . . It should be added that the red blood cells may disappear without formation of pigments. Isolated intact red blood cells may be encountered after several weeks" (Weil).

According to Weil, experiments with animals indicate that phagocytes containing red blood cells will appear on the third day. On the fifth day the first appearance of hemosiderin occurs, on the tenth day the hemosiderin is diffusively distributed in scavenger cells, on the twelfth day the granulation of hemosiderin takes place, on the eighteenth day free pigment is found outside of the cells, on the twenty-fifth day the pigment-containing corpuscles become decomposed into very fine granules and the formation of hematoidin takes place, on the forty-fifth day iron-free pigment is found in the tissues, and the cells that have contained this pigment have disappeared.

Spielmeyer, Rydberg and other investigators state that as a direct consequence of acute cerebral injury the fetal brain, like the adult brain, may already within one to two days show alter-

ations in the glia cells, particularly in the astrocytes and oligoglia. These alterations manifest as increase in the glia cell plasma, broadening of the processes, and a capacity for deeper staining. According to Weil, the microglia cells exhibit great activity in a trauma, hemorrhage or softening of the brain tissue, and in his opinion the question is still open as to whether the oligodendroglia and astrocytes can become transformed into compound granular corpuscles, as claimed by various observers.

Already within two or three days there may be present at the site of the trauma large round cells with a small half-moon-shaped nucleus situated in the periphery. In the frozen section they are seen in fat staining as compound granular corpuscles laden with fat droplets. "In paraffin or celloidin section these cells contain a meshwork, resulting from the dissolved fat droplets, like a lattice—*Gitter* in German, therefore 'gitter cells'. Such scavenger cells may also originate from resting cells of the adventitia of blood vessels" (Weil).

In connection with the intracranial traumata of newborn infants, foci of softening are very common in the region of the cerebrum, as demonstrated particularly by Schwartz in his comprehensive and detailed investigations. The softenings are encountered most frequently in the inner substance of the cerebrum, near the ventricular walls, although they also have been found e.g. in the cerebral cortex and in the region of the cerebellum. In the medulla oblongata, on the other hand, these softenings are extremely rare according to Schwartz, Rydberg and other investigators. Schwartz reports having only twice in his numerous examinations encountered a focus of softening in the medulla oblongata as a result of birth trauma. The first case was a child eleven days old who had a number of these foci in the region of the olive among other locations, and the second a child of seven weeks who showed pigment waste and cavities surrounded by glial tissue in the vicinity of the central canal. Rydberg, for his part, gives the following description based upon his studies of newborn infants: "Thus we find in some cases a very advanced softening process extended over great parts of the cerebral substance, indicating a very grave obstruction of the blood circulation

or perhaps a complete stoppage throughout considerable areas of the brain. The medullary region can never be reached by such acute destructive processes, because death will occur, owing to functional injury to the vital centre, long before the anatomical tissue change has proceeded so far."

Schwartz has found that as a result of hemorrhages in the medullary tissue of the newborn infants, displacements of the tissue immediately adjacent to the focus take place. Not only is the lumen of the blood vessel compressed but also the glia and ganglion cells in the area surrounding the hemorrhage may be pressed nearer together than in normal conditions. He has also in some cases encountered accumulations of cells around the hemorrhage.

In studying in the present investigation the pathologic consequences to the brain tissue from intracranial hemorrhages, the main attention was directed, besides to the occurrence of immediate tissue displacements, to the decomposition of red blood cells and the presence of softenings. By the latter is designated the presence of necrosed areas accompanied by the formation of fatty granule cells.

#### *Personal Observations*

As will have appeared from the detailed description given above of the microscopic hemorrhages encountered in the present investigation, no softenings were found in medullary tissue. In a few cases slight displacement of the surrounding tissue due to the hemorrhage was observed. In one case (No. 36), a child 29 hours old, there were present in association with a leptomeningeal hemorrhage large mononuclear cells, apparently macrophages, and pigment granules taken up by phagocytic cells in the region of the medulla oblongata. The absence of softenings in connection with these hemorrhages can probably be regarded as due in part to the slightness of the hemorrhages and to the structure of the network of the medullary blood vessels, with its abundant capil-

lary anastomoses. For these reasons the interferences with nutrition in connection with the hemorrhages were apparently not very great. Furthermore the infants in whom medullary hemorrhages were encountered had lived for such a short time only that for instance the formation of fatty granule cells and the decomposition of hemoglobin probably could not yet have taken place in the majority of cases. However, in association with hemorrhages in the fourth ventricle there were in a few cases signs of blood cell decomposition in infants who had lived for several days after birth, and in one case (No. 99/46) there was an increased count of glia cells under a subependymal hemorrhage opening into the fourth ventricle.

It is a recognized fact that in agony, for instance in association with conditions of asphyxia, small punctate hemorrhages may arise in various organs and in the region of the central nervous system (Schwartz, et al.). Schwartz also states that as a result of circulatory interferences due to birth traumata, a condition of for instance stasis may produce hemorrhages in the central nervous system also subsequent to birth, and therefore older infants (*i.e.* those several weeks of age) may exhibit quite fresh hemorrhages which have arisen on the basis of birth traumata. As in the present study no reactions were encountered in the majority of cases in the surrounding tissue or within the hemorrhagic area in connection with medullary hemorrhages, the time of origin of the latter cannot be inferred with any certainty. However, the hypothesis of the birth-traumatic origin of these hemorrhages is supported by the fact that no medullary hemorrhages were found in the older infants, not even those in whom prior to death respiratory difficulties were observed and who therefore presumably would have had such hemorrhages had the latter been produced by agony.

To obtain a basis of comparison for the tissue reactions seen in connection with the hemorrhages, microscopic examinations were in some cases also made of hemorrhagic foci in the region of the cerebrum.

**Case No. 109/46**, age 18 days, weight at birth 1,620 g., had a large hemorrhage in the leptomeninges of the occipital lobe. Microscopic examination

revealed the following: No hemorrhage is present in the region of the medulla oblongata or the pons, scharlach-R-hematoxylin staining brings out no fat cells. Hematoxylin-van Gieson and hematoxylin-eosin stainings of sections from the hemorrhagic point in the occipital region reveal a gross intermeningeal hemorrhage, in the center of which are seen intact and disintegrating red blood cells and accumulations of pigment. In the hemorrhagic region are also seen granules of pigment phagocytized by cells. In Prussian blue staining a part of the pigment granules stain blue (i.e. hemosiderin). In the brain tissue adjacent to the hemorrhagic area there is an abundance of large-granulated cells which enclose small droplets of fat. These cells take a strong scharlach-R-hematoxylin stain (Ill. 13).

**Case No. 19/47**, age 16 days, weight at birth 1,950 g., showed hemorrhage in the leptomeninges in the dorsal part of the left occipital lobe, left tentorial laceration, and purulent meningitis. No microscopic hemorrhage was found in the medulla oblongata or in the pons. Under the microscope is seen an extensive intermeningeal hemorrhage in the occipital region. In the hemorrhagic area a large part of the red cells are decomposed. This area also contains pigment granules, some of which are free and some phagocytized by cells. In Prussian blue staining some of the granules stain blue. Fat staining shows in the brain tissue adjacent to the hemorrhage a very few cells which contain small globules of fat.

**Case No. 22/47**, age 7 days, weight at birth 1,670 g. In the region of the left temporal lobe and occipital lobe gross hemorrhages are seen in the leptomeninges. In the region of the left lateral ventricle there is macroscopic hemorrhage seen as small dots in the brain matter. The microscopic examination reveals no hemorrhage in the tissue of the medulla oblongata or the pons. Blood is present in the fourth ventricle. In the vicinity of the lateral ventricle, near the ependyma, are seen extensive hemorrhages, with a part of the red cells in the process of decomposition. Around the hemorrhages are large numbers of small cells with hyperchromatic nucleus, the origin of which cannot be determined by histologic examination. In the marginal zones of the hemorrhages there are fairly large cells with vacuoles. The leptomeninges of the occipital lobe and the surface of the cortex show hemorrhages, in the region of which are here and there seen red cells in the process of decomposition. The margin of the hemorrhagic area is marked by a band of red acquired in the fat staining, in which the fat shows up as small, diffused, extracellular droplets. In two or three places this band forms fairly large foci.

Very distinctly recognizable changes such as described above were not found to accompany hemorrhage in the medulla oblongata and the pons. The hemorrhages in these regions were very small in size as compared with those encountered in the region

of the cerebrum. Moreover the infants affected with hemorrhages in the latter location were older than those with hemorrhages in the medulla and the pons, so that there had been time for more distinctly manifesting changes of hemorrhagic origin.

#### SUMMARY

1. The series of cases studied consists of 54 premature infants, three of whom were stillborn, and of 20 fullterm infants, six of them stillborn. All of the liveborn infants died within the first month of life. About one-half of them died within the first 24 hours and about four-fifths within the first week. One-third of the premature infant cases and one-twentieth of the fullterm infant cases had been delivered by breech presentation. The greater part of the series comprised infants suffering from respiratory disorders.
2. Macroscopic intracranial hemorrhage was encountered in the *premature infants* in 25/54 cases (46 per cent of all premature infant cases). With those weighing 1,500 g. or less the incidence of these hemorrhages was slightly higher than with the premature infants of higher weight. In operative deliveries macroscopic hemorrhage was present in 6/7 cases.
3. Microscopic hemorrhage of the medulla oblongata (occurring in the medullary tissue or in the fourth ventricle) was found in 20/54 cases (37 per cent of all premature infants). In the actual medullary tissue there was hemorrhage in 11 cases, and in the fourth ventricle in 14 cases; in five cases these hemorrhages were simultaneously present.
4. In the premature infant series the total number of macroscopic intracranial hemorrhages and of microscopic hemorrhages of the medulla oblongata alone was  $25 + 10 = 35$ . This is equal to 65 per cent of the total number of premature infant cases examined.
5. No correlation between the weight at birth and the occur-

rence of microscopic hemorrhages of the medulla oblongata could be established in the premature infant series.

6. The incidence of microscopic hemorrhages of the medulla oblongata was found to be greatest with the premature infants one to three days old. Hemorrhage in the actual medullary tissue was only present in stillborn premature infants or in those dying within three days *post partum*. In the fourth ventricle hemorrhage was encountered in stillborn infants or in those living not more than eight days.

7. As to localization, the microscopic hemorrhages of the medulla oblongata in the premature infants were situated chiefly in the environment of the fourth ventricle and in the region of the inferior olive, in addition to which hemorrhages were encountered within the fourth ventricle. The hemorrhages in the medullary tissue originated from the capillaries or the small veins and were minute in size. Within the fourth ventricle some of the hemorrhages were more extensive.

8. Presentation, operative delivery, or simultaneously present tentorial laceration had no influence upon the occurrence of microscopic hemorrhages of the medulla oblongata in the premature infants. The incidence of medullary hemorrhages was higher with premature infants born in an asphyxiated state, in whom they were present in 5/10 cases (50 per cent), than in those born in a live condition, who showed them in 14/41 cases (34 per cent).

9. The presence of microscopic hemorrhages of the medulla oblongata in the child showed no relation to parity, age, or syphilitic or nephropathic condition of the mother (maternal syphilis present in three and nephropathy in four cases; the child had hemorrhage in one case of each).

10. It was regarded as probable that the hemorrhages encountered in the medulla oblongata of the premature infants were localized in 6/54 cases (11 per cent) within the area of the respiratory center.

11. Microscopic hemorrhage in the pons was found in eight premature infant cases in association with hemorrhage in the medulla oblongata and in one case as an individual finding, making a total of 9/52 cases (17 per cent). In the majority of

cases these hemorrhages were localized in the roof or the lateral walls of the fourth ventricle and were encountered in liveborn premature infants dying within five days.

12. In ten premature infant cases selected at random in which microscopic sections were made from the region of the quadrigeminal bodies no hemorrhage was found to be present in the brain tissue.

13. Macroscopic intracranial hemorrhage was encountered in the *fullterm infants* in 13/20 cases (65 per cent). There were five operative deliveries in the series, in all of which hemorrhage was present. In four of these cases the origin was a laceration of the tentorium or the falx.

14. Microscopic hemorrhage of the medulla oblongata was found in fullterm infants in 10/20 cases (50 per cent). It was present only in stillborn infants or in those dying within three days. The macroscopic intracranial hemorrhages (13 cases) and microscopic hemorrhages in the medulla oblongata alone (4 cases) totaled 17/20 cases (80 per cent).

15. Microscopic hemorrhage was present in the pons in 3/20 cases, in all of them in association with hemorrhage in the medulla oblongata.

16. The fact of operative delivery had no effect upon the incidence of microscopic hemorrhages of the medulla oblongata. In association with tentorial laceration, microscopic hemorrhage of the medulla oblongata was present in 3/3 cases.

17. No essential difference was found to exist between premature and fullterm infants in respect to the nature and localization of microscopic hemorrhages of the medulla oblongata. As to incidence, macroscopic intracranial hemorrhage as well as microscopic hemorrhage in the medulla oblongata was more frequently encountered in the fullterm than in the premature infants.

18. In 6/39 cases blood was present in the cerebrospinal fluid withdrawn by lumbar puncture from premature infants. In three of these six cases microscopic hemorrhage was encountered in the medulla oblongata. With fullterm infants the incidence of

blood-tinted cerebrospinal fluid was 6/12 cases. Microscopic hemorrhage of the medulla oblongata was present in three of these six cases.

19. No foci of softening were observed in the premature or fullterm infants in connection with hemorrhages in the medulla oblongata or the pons. Red blood cells in the process of decomposition were seen in a few cases. It may be mentioned for comparison that in sections made from the region of the cerebrum, fatty cell formation was also encountered in association with leptomeningeal hemorrhages.

#### RESPIRATORY DISORDERS IN PREMATURE INFANTS

When observations are being made on the general condition of premature infants dying immediately *post partum* or within the first days or weeks of life it is often noted that a premature infant may be quite live at birth but within a few hours or days a worsening of the condition sets in, breathing becomes more superficial and uneven, there are cessations or other irregularities in the respiratory effort, the child becomes cyanotic, and then, as the respiratory difficulties become aggravated, the condition leads to death. The child may also be born in a state of asphyxia and die of dyspnea immediately thereafter or following a brief transient period of resuscitation. Further there may be cases in which no actual respiratory disorders are observed but the condition of the child continuously becomes weaker as respiration and the vital functions gradually cease. With children several days old, signs of infection in for instance the respiratory or digestive tracts are frequently present. It often is difficult in clinical observation to determine when the respiration of a premature infant should be regarded as regular and when a disorder should be spoken of, particularly as most premature children may show, at least immediately prior to death, movements resembling gasping respiration (*Schnappatmung*), and as for in-

stance the occasional occurrence of Cheyne-Stokes respiration is regarded by many investigators as practically physiological in the premature infant.

In speaking in the following of respiratory disorders seen in premature infants, reference is made to cases in which the irregularities observed were so manifest that they at least occasionally dominated the clinical picture and in most cases indicated special treatment procedures. According to this criterion the live-born infants in the material of this study may be classified into two groups: a) Premature infants with respiratory disorders, and b) Premature infants in whom no respiratory disorders were observed. Thirty-nine infants were regarded as belonging to the first group and twelve to the second group.

These two groups of cases are subdivided as shown in Table VII according to the children's weight at birth and age at death.

TABLE VII

*Incidence of Respiratory Disorders in Premature Infants,  
Classified according to Weight at Birth and Age*

Weight at Birth, grams	Respiratory Disorders Observed	No Respiratory Disorders Observed	Total No. of Cases
Under 1,000.....	6	6	12
1,001—1,500 .....	12	4	16
1,501—2,000 .....	13	1	14
2,001—2,500 .....	8	1	9
Total	39	12	51

Age at Death	Respiratory Disorders Observed	No Respiratory Disorders Observed	Total No. of Cases
Under 2 hours .....	6	7	13
2—24 hours .....	14	1	15
1—3 days .....	5	1	6
4—7 "	7	2	9
8—14 "	2	—	2
15—30 "	5	1	6
Total	39	12	51

As is seen from this table, distinctly recognizable respiratory disorders were observed in 39/51 cases (76 per cent of all liveborn premature infants). These disorders were the least frequent in infants of the smallest size weighing less than 1,000 g., which may at least partly be regarded a matter of interpretation, for the visual observation of respiratory disorders in the very small premature infants, whose movements of respiration may be extremely weak, is to some degree uncertain, particularly if movements of the gasping type of respiration (Schnappatmung) appearing at the very end are excluded. Apparently for the same reason, when the infants are classified according to age, the respiratory disorders are found to be less frequent in those dying within two hours than in the older age groups.

When observations are made on the irregularities of respiration in premature infants it becomes manifest that an accurate subdivision into different groups according to the kind of disorder is difficult, for the types of respiration may rapidly interchange in the same infant and disorders of several kinds may successively be present. A few examples of the respiratory disorders encountered in this study are given below.

**Case No. 93/46**, weight at birth 1,500 g., born by vertex presentation. Immediate postpartum condition of child was lively. It was hospitalized in the evening at the Children's Clinic at the age of six hours, being then in a deeply cyanosed condition and with respiration suspended. Resuscitation gradually set in after administration of oxygen and stimulants. There were several asphyctic attacks in the course of the night, with the face very dark and respiration interrupted. The attacks were met with oxygen and breathing was fairly regular in the intervals. The cyanosis became aggravated and the patient died on the following day at the age of 18 hours. Postmortem examination revealed partial pulmonary atelectasis and intracranial hemorrhage. At microscopic examination no hemorrhage was found in the medulla oblongata, where the capillaries were fairly heavily blood-filled.

**Case No. 102**, weight at birth 2,160 g., age 24 hours, born by extraction of breech presentation. The child was deeply asphyxiated at birth, with a heartbeat of 40 to 50 per minute. During the first two or three minutes respiration was totally absent, followed by superficial breaths four to five times a minute. Half an hour after administration of artificial respiration and insufflation, breathing improved and attained a rate of about 30 per minute. The child uttered faint sounds, and during the next few

hours respiration was fairly regular but at rates varying from 35 to 70 per minute. Brief interruptions of breathing (10 to 15 seconds) were observed later, accompanied by a cyanotic facial hue. Respiration was thereafter superficial, uneven and irregular and there were several cessations of respiration and attacks of cyanosis. The postmortem finding was an extensive intracranial hemorrhage originating from a tentorial laceration and extending not only to the convexity of the cerebrum but also to the basal part of the brain as far as the region of the medulla oblongata. The lungs were air-filled. Microscopic hemorrhage was present in the medulla and the pons and the capillaries were very full.

**Case No. 206**, weight at birth 780 g., age 1 day, born by vertex presentation. No signs of life were at first observable in the child, who was deeply cyanosed. About 15 minutes later resuscitation set in, the child cried about one hour after birth, and respiration was weak and irregular. It was later of the Cheyne-Stokes type at a rate of approximately one per second; a respiratory phase lasting from 20 to 30 seconds was followed by a pause of about 10 to 15 seconds. The color was good, the child uttered faint sounds now and then. Before the end the child became completely cyanosed, and respiration became weaker and more superficial. Postmortem examination disclosed an extensive leptomeningeal hemorrhage on the inferior surface of the cerebellum and in the environment of the medulla oblongata. Blood filled the cerebral ventricles. Air content of right lung was diminished. Microscopic examination showed the capillaries of the medulla oblongata and the pons to be heavily blood-filled; there was blood in the fourth ventricle and effusions in the leptomeninges in the region of the medulla and the pons.

**Case No. 62**, weight at birth, 1,700 g., age 14 hours, born by vertex presentation. Child was lively at first but some hours later began to fail, face turned a dark cyanotic hue and respiration was labored, with a moan at each breath. Respiration became later fairly regular but continued to be labored, child was still cyanotic, and constant administration of oxygen was necessary. No macroscopically recognizable intracranial hemorrhage was found at autopsy but microscopic examination showed that the capillaries in the region of the medulla oblongata and the pons were rather full, and there was much blood in the fourth ventricle and an effusion in the medulla oblongata on the floor of the fourth ventricle.

The description of cases given above and in Table XI shows that respiratory interruptions of longer or shorter duration may take place in a premature infant, respiration being at times fairly even and regular and at times faint and superficial. With some children it was constantly dyspneic and panting. Cyanosis might be present either as a permanent condition or in the form of at-

tacks. In some cases there was cough or copious discharge of mucus from the nose and mouth. The rate of breathing was liable to vary from complete cessation of respiration to as much as 200 per minute.

These cases were offset by others in which actual respiratory difficulties were not encountered but respiration gradually weakened and slowed down.

Ten of the premature infants suffering from respiratory difficulties were already asphyctic at birth; four of these died within two hours without starting spontaneous respiration except for a few superficial agonal movements, the primary condition of asphyxia persisting until death. In other cases the primary asphyxia was succeeded by fairly good respiration.

If, on the basis of the observations, an effort nevertheless is made to classify the respiratory disorders encountered in the premature infants according to the type of respiration *primarily* seen, the following tabulation will be obtained:

TABLE VIII

*Respiratory Disorders in Premature Infants, Classified according to Primary Type of Respiratory Disturbance, and their Correlation with Microscopic Hemorrhages of the Medulla Oblongata*

Primary Feature of Respiratory Disorders	Respiratory Disorders Observed	Microscopic Hemorrhage Present in Medulla Oblongata	No Microscopic Hemorrhage Present in Medulla Oblongata
	No. of Cases	No. of Cases	No. of Cases
a) Interruptions of respiration; attacks of cyanosis .....	15	5	10
b) Respiration weak, superficial, irregular, or periodic .....	15	7	8
c) Child agonal (heart functioned; no respiratory effort, or some superficial respirations)	4	1	3
d) Inspiration difficult; moaning respiration ..	5	2	3
e) No respiratory disorders seen .....	12	4	8
Total	51	19	32

- a) Cases No. 6, 38, 63, 102, 203 and 10, 20, 37, 202, 207, 93/46, 94/46, 95/46, 97/46, 30/47.
- b) Cases No. 19, 36, 99/46, 22/47, 33/47, 206, 39 and IV, 65, 67, 103, 108, 109/46, 15/47, 19/47.
- c) Cases No. 26 and 3, 7, 11.
- d) Cases No. 62, 104/46 and 13, 64, 66.
- e) Cases No. 1, 16, 30, 111 and II, 14, 21, 25, 34, 105, 110, 204.

A large number of transitional forms of respiration types were seen, in groups a) and b) in particular.

CORRELATION BETWEEN PATHOLOGIC FINDINGS AND RESPIRATORY DISORDERS OBSERVED IN PREMATURE INFANTS

*Microscopic Hemorrhages of the Medulla Oblongata and the Pons*

Microscopic hemorrhage was encountered in the *medulla oblongata* in 15/39 cases (38 per cent) of premature infants suffering from respiratory disorders (Table IX).

**TABLE IX**  
*Pathologic Changes in Premature and Fullterm Infants, Classified according to Respiratory Disorders Observed*

		No. of Cases	Microscopic Hemorrhage in Medulla Oblongata	Microscopic Hemorrhage in Pons	Macroscopic Intracranial Hemorrhage (Hemorrhage in Environment of Medulla Oblongata)	(Laceration of Falx)	(Laceration of Tentorium)	Other Hemorrhages	Pulmonary Atelectasis	Pneumonia
<b>Premature Infants:</b>										
Respiratory disorders observed in infants born in:										
a) live condition .....	29	10	3	11	(3)	—	(4)	7	12	6
b) asphyctic condition ..	10	5	4	8	(2)	(1)	(2)	2	6	1
Total	39	15	7	19	(5)	(1)	(6)	9	18	7
No respiratory disorders observed .....										
Stillborn .....	12	4	2	5	—	—	(1)	4	7	—
Stillborn .....	3	1	—	1	—	—	—	3	3	—
Total Premature Infants	54	20	9	25	(5)	(1)	(7)	16	28	7
<b>Fullterm Infants:</b>										
Respiratory disorders observed in infants born in:										
a) live condition .....	5	2	1	3	—	—	—	2	1	1
b) asphyctic condition ..	6	4	1	5	(2)	(1)	(2)	4	2	—
Total	11	6	2	8	(2)	(1)	(2)	6	3	1
No respiratory disorders observed .....										
Stillborn .....	3	1	1	1	—	—	—	1	1	—
Stillborn .....	6	3	—	4	(3)	(2)	(1)	2	6	—
Total Fullterm Infants	20	10	3	13	(5)	(3)	(3)	9	10	1

Hemorrhages in connection with cases listed in parentheses are included in the macroscopic intracranial hemorrhages.

In nine cases the hemorrhage was situated in the actual medullary tissue, and in five of these it was regarded as probably localized within the area of the respiratory center (cases No. 6, 26, 62, 102 and 203). Differentiating between the children born in a live condition and those born in a state of asphyxia it was found that hemorrhages of the medulla oblongata were present in the former in 10/29 cases (34 per cent) and in the latter in 5/10 cases (50 per cent). The latter category showed hemorrhage in the actual medullary tissue in four cases, and in two of these (cases No. 26 and 102) it probably was situated in the area of the respiratory center.

No variations could be discerned in the character of the respiratory disorders when the hemorrhages were localized in different parts of the actual medullary tissue or in the fourth ventricle. The latter hemorrhages occurred also in infants over three days old.

Distinct differences could not be seen in the nature of the respiratory disorders when comparing those of infants with microscopic hemorrhage in the medulla oblongata and those of infants in the same age group (not over eight days old) in whom such hemorrhages were not present, for similar respiratory disorders were seen in both groups (Tables VII and VIII). On the other hand, in children several weeks old in whom no microscopic hemorrhage was encountered in association with respiratory disorders, signs of infection of the respiratory tract were in some cases found.

With premature infants suffering from respiratory disorders the blood content of the medullary capillaries was high or moderately high in 34/39 cases and scant in 5/39 cases only. In all cases of microscopic hemorrhage of the medulla the capillaries were abundantly blood-filled.

In association with the respiratory disorders microscopic hemorrhage in the pons was encountered coincidentally with medullary hemorrhage in six premature infant cases and as a single finding in one case (case No. 65). With the children born in a condition of asphyxia hemorrhages of the pons were present in 4/10 cases (40 per cent) and with those born in a live condition in 3/27 cases

(11 per cent). Microscopic examination was not made of the pons in the case of two premature infants. Except for one case the hemorrhages of the pons were situated in the roof or the lateral walls of the fourth ventricle, which are regions not associated, as far as is known, with the control of the respiratory effort.

#### *Macroscopic Intracranial Hemorrhages*

As is further seen from Table IX, macroscopic intracranial hemorrhage was found to be present in 19/39 cases (49 per cent) of premature infants suffering from respiratory difficulties. These cases include seven duraduplicate, ten leptomeningeal and two intraventricular hemorrhages. A noteworthy fact is that among the seven tentorial lacerations found in the entire series of premature infant cases a collateral finding of respiratory disorders was made in six of them. In one of the latter cases with tentorial laceration and in 4 other cases of respiratory disorders extensive hemorrhage was encountered in the environment of the medulla oblongata.

In association with the respiratory disorders a severe or moderately severe leptomeningeal edema was present in 23/39 cases. However, in the region of the medulla oblongata it was fairly slight in the majority of cases.

#### *Pulmonary Changes*

Among the other pathologic findings in premature infants suffering from respiratory difficulties the most important group comprised changes in the lungs, encountered in 25/39 cases (64 per cent). Eighteen of these were cases of pulmonary atelectasis and 7 of pneumonia. A detailed description of the pulmonary changes does not come within the scope of the present study but it may be briefly mentioned that in two cases (No. 97/46 and 15/47), in the former of which the macroscopic examination disclosed atelectasis and in the latter no specific finding, pneumonic changes were found at microscopic examinations made in con-

nnection with another study (Ahvenainen 1948). It therefore may be probable that the number of pneumonia cases in this material was actually greater than indicated above by the autopsy findings. In thirteen cases of premature infants suffering from respiratory disorders, macroscopically recognizable intracranial hemorrhage was found in addition to the pulmonary changes.

#### *Hemorrhages in Other Organs*

In association with respiratory disorders extracranial hemorrhages were encountered in 9/39 cases in various organs, as for instance on the outer surface of the thymus or in the pericardium, pleura, liver or kidneys. In one of these cases (case No. 7) hepatic laceration was present, resulting not only in a subcapsular hematoma but also in profuse hemorrhage into the abdominal cavity (intracranial hemorrhage and pulmonary atelectasis were also present in the same infant). In the other cases the hemorrhages were slight petechiae, which apparently had no etiological bearing upon the respiratory disorders.

Taking into account only those cases where premature infants with respiratory disorders showed microscopic hemorrhage in the medulla oblongata it will be seen that a collateral finding was macroscopic intracranial hemorrhage in 8/15 cases, in four of which such hemorrhage was present also in the vicinity of the medulla oblongata (cases No. 36, 38, 102 and 206, Table XI a). Pulmonary changes, i.e. pneumonia and atelectasis, were also found in 8/15 cases. In a total of 11/15 cases there was either macroscopic hemorrhage (3 cases), pulmonary changes (3 cases), or both (5 cases). In 4/15 cases only no macroscopically recognizable pathologic changes in other organs, apart from leptomeningeal edema, were encountered in addition to the microscopic hemorrhage in the medulla oblongata. In two of these cases (No. 63 and 203) there was microscopic hemorrhage also in the pons, and in one case (No. 62) opening of the skull only was permitted and therefore the presence of for instance pulmonary changes cannot be excluded with certainty.

*There thus remains only one case (No. 39) in which the microscopic hemorrhage in the medulla oblongata constituted the only pathologic finding.* It therefore seems probable that in cases where microscopic hemorrhage of the medulla oblongata is found in association with respiratory disorders in premature infants, collateral findings of changes in other organs will also generally be made, consisting usually of either macroscopic intracranial hemorrhage or pulmonary changes, or frequently of both. Worthy of notice is also the fact that in the total of five cases of premature infants with respiratory difficulties in whom macroscopic hemorrhage was present in the environment of the medulla oblongata, four cases also showed microscopic hemorrhage in the medulla.

*Cases in which no microscopic hemorrhage of the medulla oblongata was encountered in association with respiratory disorders totaled 24/39, or 62 per cent (Table XI c).* In twenty of these cases findings were made either of macroscopic intracranial hemorrhage only (3 cases), pulmonary changes only (9 cases), or both (8 cases). In four cases (No. 64, 108, 202 and 95/46) no pathologic changes with the exception of leptomeningeal edema or of a few small ecchymoses were encountered. Further collateral findings in premature infants in this group were enteritis coincidentally with bilateral pneumonia, and enteritis in one case and meningitis in another case in association with intracranial hemorrhage.

From the entries in Tables IX, XIb and XI d on *premature infants in whom no respiratory disorders were observed* it will be noted that microscopic hemorrhage in the region of the medulla oblongata was present in 4/12 cases (33 per cent). In three cases the hemorrhage was situated in the fourth ventricle and in one case in the medullary tissue. In the last mentioned instance (case No. 30) it was localized in the region of the reticular formation. In association with two cases of medullary hemorrhage the blood content of the capillaries was fairly copious, whereas in all the other cases where no disorders of respiration were observed it was scant (10/12 cases). Microscopic hemorrhage of the pons was encountered in two cases. In one of the cases of microscopic medullary hemorrhage there was a simultaneous finding of macro-

scopic intracranial hemorrhage and in two cases of pulmonary atelectasis. Macroscopic intracranial hemorrhage was present in a total 5/12 cases (42 per cent) but was not encountered in the environment of the medulla oblongata. Pulmonary atelectasis was present in 7/12 cases (58 per cent), in three of which there was also macroscopic intracranial hemorrhage. Additional findings were some slight petechiae in various organs.

In *stillborn premature infants* (Tables IX and XI e) microscopic hemorrhage of the medulla oblongata and macroscopic intracranial hemorrhage were each found in one out of the three cases. The incidence of hemorrhage was therefore not higher with these premature infants than with the liveborn.

#### SUMMARY

##### *Premature Infants with Respiratory Disorders*

1) Respiratory disorders were encountered in the present investigation in 39/51 cases (76 per cent) of the liveborn premature infants.

2) In association with the respiratory disorders microscopic hemorrhages in the medullary tissue or the fourth ventricle were encountered in 15/39 cases (38 per cent). The hemorrhage was situated in the medullary tissue in 9/39 cases, and in five of these cases (5/39) it was regarded as probably situated within the area of the respiratory center. No difference according to the localization of the microscopic medullary hemorrhages was observable in the character of the disorders. The hemorrhages were only encountered in children dying within the first eight days after birth.

3) The occurrence of microscopic hemorrhages in the medulla oblongata was higher (5/10 cases, 50 per cent) with liveborn premature infants delivered in a state of asphyxia than with those delivered in a live condition (10/29 cases, 34 per cent).

4) In 24/39 cases (62 per cent), no microscopic hemorrhage

was encountered in the medulla oblongata in association with the respiratory disorders. Differences were not seen in the nature of these disorders when compared with those present in premature infants of the same age group showing hemorrhage in the medulla oblongata. Signs of infection of the respiratory tract were in most cases present in premature infants over eight days of age.

5) Microscopic hemorrhage was encountered in the pons coincidentally with that in the medulla oblongata in six cases and as a sole finding in one case, or in a total of 7/37 cases (19 per cent of the cases in which microscopic examination of the pons was also made).

6) Macroscopically recognizable intracranial hemorrhage was present in association with respiratory disorders in 19/39 cases (49 per cent). In five of these cases macroscopic hemorrhage was encountered also in the environment of the medulla oblongata.

7) The presence of pneumonia and pulmonary atelectasis was established in 25/39 cases (64 per cent).

8) In addition to a finding of microscopic hemorrhage of the medulla oblongata (15 cases) in premature infants suffering from respiratory disorders, simultaneous findings were made of macroscopic intracranial hemorrhage (3 cases), macroscopic intracranial hemorrhage and pulmonary changes (5 cases), pulmonary changes only (3 cases), or no macroscopic pathologic changes (4 cases). In one case only the microscopic hemorrhage encountered in the medulla oblongata constituted the sole pathologic finding.

9) In the cases where no finding of microscopic hemorrhage in the medulla oblongata was made in association with the respiratory disorders (24 cases) there was a finding of macroscopic intracranial hemorrhage (3 cases), macroscopic intracranial hemorrhage and pulmonary changes (8 cases), or pulmonary changes only (9 cases). In four cases no macroscopic pathologic changes were encountered with the exception of leptomeningeal edema.

10) In 34/39 cases (87 per cent) the blood content of the capillaries was remarkably abundant in association with the respiratory disorders.

*Premature Infants in whom No Respiratory Disorders  
Were Observed*

11) No respiratory disorders were observed in the present investigation in 12/51 cases (24 per cent) of liveborn premature infants examined.

12) Microscopic hemorrhage of the medulla oblongata was found to be present in 4/12 cases (33 per cent) of infants in whom no respiratory disorders were observed. In addition to hemorrhage of the medulla, microscopic hemorrhage was present in the pons in 2/12 cases.

13) Macroscopic intracranial hemorrhage was present in 5/12 cases (42 per cent) of premature infants in whom respiratory disorders were not observed. None of the macroscopic hemorrhages were localized in the environment of the medulla oblongata. Pulmonary atelectasis was present in 7/12 cases (58 per cent).

14) The blood content of the medullary capillaries was scant in 10/12 cases.

*It thus is seen that the incidence of microscopic hemorrhages both in the medulla oblongata and in the pons was slightly higher with the premature infants suffering from respiratory disorders than with those in whom no disorders of this nature were observed. The capillary blood content was also greater with the former. Likewise the incidence of macroscopic intracranial hemorrhages and pulmonary changes was higher with the premature infants with respiratory disorders, even if the difference was slight. Macroscopic hemorrhage in the vicinity of the medulla oblongata was present only in premature infants with respiratory disorders. The incidence of microscopic hemorrhages in both the medulla oblongata and the pons was higher with the premature infants with disorders who were born in an asphyxiated condition than with the premature infants with disorders who were delivered in a live condition. In nearly all cases of microscopic hemorrhage in the medulla oblongata, pathologic changes were also encountered in other organs.*

## RESPIRATORY DISORDERS IN FULLTERM INFANTS AND THEIR CORRELATION TO PATHOLOGIC FINDINGS

In the series of liveborn fullterm infants comprising 14 cases, respiratory disorders were present in 11 infants. They are classified according to age in Table X.

TABLE X

*Incidence of Respiratory Disorders in Fullterm Infants, Classified according to Age and Postpartum Condition*

Age	Respiratory Disorders Observed			No Respiratory Disorders Observed	Total No. of Cases
	Asphyxiated at Birth	Live at Birth	Total		
Under 2 hours . . . 3		1	4	—	4
2-24 hours . . . 1		1	2	—	2
1-3 days . . . 1		2	3	3	6
4-7 " . . . —		—	—	—	—
8-14 " . . . —		1	1	—	1
15-30 " . . . 1		—	1	—	1
Total 6	5	11	3	14	

Fullterm infants dying within two hours include three children who were born in a deeply asphyxiated condition and did not start spontaneous respiration (agonal). The fourth child who died at this age showed at first satisfactory respiration, but after the lapse of a few minutes respiration ceased whereas the heart continued to function for some 30 minutes. The respiration of children suffering from respiratory disorders in the other age groups was either irregular, slow and disconnected, or panting, and there were cessations of respiration or attacks of cyanosis, as shown in Tables XI f and XI h. Three of these children were asphyctic at birth.

The fullterm infants with respiratory disorders included one born by brow presentation, one by face presentation, one by for-

ceps delivery, and one with the cord twined twice around the neck.

*In association with respiratory disorders fullterm infants showed microscopic hemorrhage of the medulla oblongata* in 6/11 cases (54 per cent) (Table IX). In all of these cases hemorrhage was present in the fourth ventricle; in three cases there was hemorrhage also in the actual medullary tissue (cases No. 27, 31 and 32). It was regarded as probable that the hemorrhage was localized within the area of the respiratory center in one case (No. 32). Microscopic hemorrhage was present in the pons in two cases, both coincidentally with medullary hemorrhage; one being in the roof of the fourth ventricle and one beneath the pia.

*In association with the respiratory disorders of the fullterm infants macroscopic intracranial hemorrhage* was encountered in 8/11 cases (73 per cent) (Table IX). Two of these infants showed a tentorial laceration. In two cases there was hemorrhage around the medulla oblongata; one of them was a tentorial laceration case. *Pneumonia* (1 case) and *pulmonary atelectasis* (3 cases) were present in a total of 4/11 cases (36 per cent), in two of which the atelectasis was found simultaneously with macroscopic intracranial hemorrhage. *Hemorrhage in other organs* was encountered in association with respiratory disorders in 6/11 cases. In one of these cases there was gross hemorrhage in the liver (case No. III) and in another case hemorrhage was also present in the pleural cavity (case No. 107). Minute effusions of blood in various organs were also encountered in some cases.

Coincidently with microscopic hemorrhage of the medulla oblongata the fullterm infants with respiratory disorders had macroscopic intracranial hemorrhage in four cases. A tentorial laceration was present in two of these cases, in one of which there was hemorrhage also around the medulla. A simultaneous finding with microscopic hemorrhage of the medulla was pulmonary atelectasis in three cases.

Fullterm infants in whom *no respiratory disorders were seen* had microscopic hemorrhage in the medullary tissue in 1/3 cases, the same child also showing hemorrhage in the pons and pulmonary atelectasis (case No. 4, Table XI g). In the other two infants

(No. 24 and 28, Table XI i) macroscopic intracranial hemorrhage was present in one case and hemorrhage in the liver and the pleural cavity in the other case.

In stillborn fullterm infants microscopic hemorrhage of the medulla oblongata was encountered in 3/6 cases and macroscopic intracranial hemorrhage in 4/6 cases (Tables IX and XI j). These hemorrhages were simultaneous in two cases.

To summarize it can be said that also fullterm infants suffering from respiratory disorders showed a higher incidence of microscopic hemorrhages of the medulla oblongata (6/11 cases, or 54 per cent), macroscopic intracranial hemorrhages (8/11 cases, 73 per cent), and pulmonary changes (4/11 cases, 36 per cent) than fullterm infants in whom respiratory disorders were not observed (1/3 cases each). Fullterm infants with respiratory disorders who were born in a state of asphyxia showed more hemorrhages, both microscopic medullary and macroscopic intracranial, than those born in a live condition (Table IX). Macroscopic hemorrhage was also encountered in the environment of the medulla oblongata in association with respiratory disorders in fullterm infants.

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## IV

### DISCUSSION

It was stated above that the object of the present investigation is to shed further light upon the occurrence of microscopic hemorrhages of the medulla oblongata and the pons in premature infants dying within the first month after birth and to attempt to determine whether such hemorrhages, if found, are of etiologic significance in the occurrence of respiratory disorders in premature infants. As appeared from the review of the literature, the regulation of the respiratory mechanism is dependent upon a great variety of factors, and moreover opinions still diverge to some extent in regard to the exact location of the chief respiratory center and its structure and activity. These circumstances tend to cause difficulty in making inferences from the observations made, when estimating the significance of hemorrhages in the causation of respiratory disorders.

As seen from the foregoing report on the results of this investigation, 20 cases (37 per cent) in the total series of 54 premature infants, including three stillborn, showed microscopic hemorrhage in the medulla oblongata. In 11/54 cases (20 per cent) the hemorrhage was localized in the actual medullary tissue, whereas in the other cases it was in the fourth ventricle. It was regarded as probable that in 6/54 cases (11 per cent of the total material) the hemorrhage was situated within the area of the respiratory center.

At microscopic examination of the pons in 52 cases, minute effusions of blood were found coincidently with hemorrhage in the medulla oblongata in 8 cases and as a sole finding in 1 case,

or in a total of 9/52 cases (17 per cent). Examinations made of the region of the quadrigeminal bodies revealed no microscopic hemorrhages in the 10 cases examined.

Except for one somewhat extensive leptomeningeal hemorrhage (case No. 36), all the hemorrhages present in the tissue of the medulla and the pons were minute, and foci of softening were not encountered in association with them. The hemorrhages present in the fourth ventricle were in some cases visible even to the naked eye.

No correlation was found to exist between microscopic hemorrhages of the medulla oblongata and the pons on the one hand and the age and parity of the mother, operative intervention at delivery, or presentation of the child at birth on the other hand. The incidence of these hemorrhages in the different weight groups was also approximately the same. With children born in a condition of asphyxia the incidence of medullary hemorrhages was higher (5/10 cases, 50 per cent) than with those born in a live conditions (10/29 cases, 34 per cent). In reviewing the results from the standpoint of age of the children it was found that microscopic hemorrhage was only present in the medullary tissue of stillborn premature infants or those dying within the first three days after birth, and in the fourth ventricle of stillborn premature infants or those living eight days at the most. Hemorrhage in the pons was only present in liveborn premature infants surviving not more than five days.

In the series of 20 fullterm infants examined as a control material microscopic hemorrhage was encountered in the medulla oblongata in 10/20 cases (50 per cent), and was situated in the actual medullary tissue in 7/20 cases (35 per cent). It was regarded as probable that the hemorrhage was localized within the area of the respiratory center in 3/20 cases (15 per cent). Except for a somewhat higher frequency of microscopic hemorrhages in the medulla oblongata, the results of the study on fullterm infants did not greatly differ from those obtained on the premature cases. Of particular interest is the observation that whereas macroscopic intracranial hemorrhage was present in all the cases of operative delivery of fullterm infants (5 cases), microscopic

hemorrhage in the medulla oblongata was only present in two of these cases. Thus even a severe intracranial trauma did not in itself necessarily imply the occurrence of a microscopic medullary hemorrhage.

Distinctly recognizable disorders of the respiration were encountered in the investigation in 39/51 cases (76 per cent) of liveborn premature infants, even if the remaining 12 cases include a number of infants in which the possible presence of occasional respiratory disorders cannot be excluded with certainty. Microscopic hemorrhages in the medulla oblongata were more frequently present in the premature infants suffering from respiratory disorders (15/39 cases, 38 per cent) than in premature infants in whom respiratory disorders were not observed (4/12 cases, 33 per cent). Premature infants with respiratory disorders who were in an asphyxiated condition already at birth showed microscopic medullary hemorrhage in 5/10 cases (50 per cent). In nearly all the cases of respiratory disorders a greater blood content was seen in the capillaries of the medulla and the pons than in the cases in which no disorders of this kind were observed.

In evaluating the etiologic interrelation between microscopic hemorrhages of the medulla oblongata and respiratory disorders in premature infants, note is firstly to be made of the fact that such hemorrhages were encountered in 15/39 cases only, or in 38 per cent of the premature infants suffering from respiratory disorders, and that in 5/39 cases only (13 per cent) the hemorrhage could be regarded as probably localized within the area of the respiratory center. In 62 per cent of the cases, therefore, the disorders seen in the respiration could not be a result of microscopic hemorrhage of the medulla oblongata, as such hemorrhage was not present in the child. In estimating the importance of medullary hemorrhages in cases where microscopic hemorrhage was found it should, however, be kept in mind that the occurrence of a small amount of bleeding does not in itself necessarily imply a serious interference with the functions of the brain tissue, particularly when the subject is a premature child whose central nervous system is not yet complete in its anatomic and physiologic development. The hemorrhages encountered in the

medullary tissue were so minute that consequences such as for instance interferences with the nutrition of the ganglion cells can hardly have occurred. The respiratory center occupies a fairly large area in the medulla oblongata, and as it moreover is believed to be bilateral and the two halves connected by decussating pathways, a limited hemorrhage situated at a given point of the respiratory center apparently does not essentially involve serious disorders in the respiration, especially if the hemorrhage is localized in an area of minor importance. On the other hand, the investigator can have no knowledge of the character of possible trauma to which the medulla oblongata may have been subjected at delivery or of the possible occurrence of also other injury more difficult to recognize than a small hemorrhage. The frequent occurrence of interferences in the medullary blood circulation in connection with respiratory disorders is revealed not only by the presence of hemorrhages but also by the greater than normal capillary blood content, which may even manifest as a severe stasis. The inference might be made that in connection with hemorrhages in the fourth ventricle, and at least in cases where the hemorrhage is fairly large, harmful pressure action upon the mechanism of the respiratory center might take place.

The microscopic hemorrhages encountered in the pons apparently have had no appreciable etiologic bearing upon the respiratory disorders in the present cases, for the hemorrhages were small in number and size, and the chief respiratory center is not believed to extend to the pons. Moreover the microscopic hemorrhages seen in the pons were almost without exception situated in the roof or the lateral walls of the fourth ventricle, and those areas do not, as far as is known, affect the respiratory effort.

In evaluating the effect of microscopic hemorrhages of the medulla oblongata upon respiratory disorders in premature infants, attention should also be given to any other pathologic changes encountered. According to the results obtained in the present investigation, such changes are primarily macroscopically visible intracranial hemorrhages and alterations in the lungs, such as pneumonia and pulmonary atelectasis in particular.

In the premature infants suffering from respiratory disorders in whom macroscopic intracranial hemorrhage was encountered (19/39 cases), microscopic medullary hemorrhage was simultaneously present in 8/39 cases. Microscopic hemorrhage of the medulla oblongata without a collateral finding of macroscopic intracranial hemorrhage was seen in 7/39 cases, and macroscopic intracranial hemorrhage only without a coincident finding of microscopic medullary hemorrhage was seen in 11/39 cases. It is apparent from this that respiratory disorders may occur as a result of, or in association with, macroscopic intracranial hemorrhage also in the absence of coincident microscopic hemorrhage of the medulla oblongata. In cases where simultaneous findings of both microscopic medullary hemorrhage and macroscopic intracranial hemorrhage are made, determination cannot therefore be made, with any degree of certainty, of the part played by the macroscopically recognizable hemorrhage or the associated trauma in the causation of the respiratory disorder as a factor auxiliary to the microscopic medullary hemorrhage. This is especially true if profuse hemorrhage is also present in the immediate vicinity of the medulla oblongata.

Pneumonia and pulmonary atelectasis in association with respiratory disorders was encountered in the premature infant series in 25/39 cases (64 per cent). In a part of these cases a collateral finding was made either of microscopic hemorrhage in the medulla oblongata, of macroscopic intracranial hemorrhage, or of both. There also were cases in which no pathologic changes other than those seen in the lungs were encountered in premature infants suffering from respiratory disorders, as well as cases in which these infants showed no pathologic changes other than some minute petechiae in various organs. *Taken as a whole these findings indicate that the respiratory disorders encountered in the premature infants were not strictly confined to any given pathologic change seen in these infants.*

To exemplify the difficulty of determining either on the basis of the clinical picture or of the pathologic findings the true causative factor in the respiratory disorders seen in a premature

infant the triple delivery included in the present series of cases is cited (cases No. 36, 37 and 38, Ill. 14). These three infants were born by foot presentation (case No. 38 after internal podalic version and extraction) and their immediate postpartum condition was lively. Case No. 37 (weight at birth 1,150 g.) and case No. 38 (1,310 g.) lived for about 14 hours. No variances were seen in the clinical picture of the two infants, and similar interruptions of respiration and attacks of cyanosis were present in both. In case No. 37 no macroscopic intracranial hemorrhage or microscopic medullary hemorrhage was encountered at postmortem examination; the pulmonary finding was mild atelectasis. In case No. 38 the autopsy revealed extensive hemorrhage in the environment of the medulla oblongata, blood in the cerebral ventricles, microscopic hemorrhage in the medulla oblongata (fourth ventricle), and marked pulmonary atelectasis. The third child (case No. 36, weight at birth 1,080 g.), who lived for 29 hours and suffered from difficult respiration during the last two hours only, was found to have a heavy blood coagulum surrounding the medulla and occluding the foramen magnum, blood in the cerebral ventricles, and microscopically seen blood in the medulla oblongata (fourth ventricle and leptomeninges), whereas the air content of the lungs was fairly high. No definite conclusion can be drawn concerning the primary cause of the respiratory disorders in these three cases. Should a premature infant's respiratory disorders chiefly be a result of the immaturity of the respiratory center, as stated by e.g. Peiper, it could have been expected that the smallest of these three infants, in whom moreover the most marked pathologic changes were encountered, would have shown the most distinct respiratory disorders and the shortest life. Actually, however, the opposite was the case.

In reviewing the results in the cases of liveborn premature infants in whom no clinical finding of respiratory disorders was made we also find that macroscopic intracranial hemorrhage and microscopic hemorrhage in the region of the medulla as well as pulmonary atelectasis were present, even if these changes were less frequently seen than in premature infants suffering from respiratory disorders. These findings indicate nevertheless that

distinctly manifesting respiratory disorders need not always be associated with intracranial hemorrhages or pulmonary changes.

The fullterm infants in the present series, in whom respiratory disorders were encountered in 11/14 cases (78 per cent), also showed in connection with respiratory disorders more frequent microscopic hemorrhage of the medulla oblongata (54 per cent), macroscopic intracranial hemorrhage (73 per cent), and pulmonary atelectasis (36 per cent) than the fullterm infants in whom no respiratory disorders were seen (1/3 cases each).

In attempting to shed light upon the correlation between intracranial hemorrhages of birth-traumatic origin and respiratory disorders seen in premature infants, mention must be made of the opinion of certain investigators (*e.g.* Peiper) that a lesion in the cerebrum is *per se* devoid of significance for the vital functions of the child provided the injury does not extend to the cerebral base. It also has been stated (Beneke 1940) that a cerebral trauma may result in arteriospasm, which in turn may lead to ischemia, necrosis and hemorrhage also in regions distant from the point of trauma. According to Brock (1943) a premature child shows a remarkably great tendency to asphyxia, and asphyxia at delivery renders the brain extremely receptive to the effects of external trauma and leads for instance to edema and hemorrhage in the tissues, which in turn brings about various degrees of local or general injury to these tissues. So *e.g.* Hassin (1943) states that the changes present in association with traumatic cerebral lesions are a result not only of mechanical but also of pathophysiologic factors, such as for instance interference in the nutrition of the ganglion cells, nerve fibres and glia cells; this interfering action is aggravated by edema in particular. In the opinion of some authors an intracranial hemorrhage is to be regarded merely as an indication of the occurrence of a birth trauma (Kermauner, Föderl, *et al.*).

In consideration of the finding in the present material of macroscopic intracranial hemorrhage in 19/39 cases of premature infants suffering from respiratory disorders, there exists at least in these cases, according to the last mentioned theory, a very pronounced birth trauma, the manifestation of which is the hemor-

rhage. It must be regarded as very probable that these 19 cases also include some in which the birth trauma has, in addition to causing a macroscopic intracranial hemorrhage, also injured the medulla oblongata in such a manner as to bring about either microscopically visible hemorrhage or anatomic changes which could not be recognized.

Hausbrandt and Meier, Heidler, and other investigators have emphasized the significance of pressure exerted upon the cerebral base in connection with tentorial laceration, as the protective function of the tentorium is then lost. The importance of this factor is also demonstrated by the finding in the present investigation that out of the seven tentorial lacerations in the total series of premature infants respiratory disorders were observed in six cases, in two of which a further postmortem finding was microscopic hemorrhage in the medulla oblongata and in one case in the pons. A tentorial laceration was present also in two liveborn fullterm infants and in both cases there were respiratory difficulties and microscopic hemorrhage in the medulla oblongata.

As was seen in connection with the presentation of the results, the infants examined include cases in which, even in association with severe cases of birth trauma and extensive macroscopic intracranial hemorrhage, only scant bleeding was found in the medullary tissue, and cases in which no medullary hemorrhage whatsoever was present. On the other hand it is a known fact that as a consequence of birth trauma, hemorrhages for instance in the fundus of the eye may be very frequent but that in most cases these soon disappear without causing further injury. Under the same laws of pressure it might be assumed that the act of parturition could also cause such bleeding in the medulla oblongata as might partly disappear without producing graver symptoms. The medullary tissue being firm in texture, it apparently offers poor conditions for larger hemorrhages.

In view of the limited size of the medullary hemorrhages it appears probable that a microscopic hemorrhage in the medulla oblongata generally does not in itself produce disorders in respiration, but its presence is an evidence of a tissue injury which may exert a harmful effect upon, for instance, the activity of

the respiratory center situated in the medulla oblongata. The results reached in the investigation described herein indicate that there probably exist also other etiological factors, external to both the medulla oblongata and the pons, in the respiratory disorders of premature infants, and that in the majority of cases several causes are simultaneously recognizable which conjointly may lead to the manifestation of respiratory disorders.

## SUMMARY

An attempt has been made in this investigation to study the occurrence of microscopic hemorrhages of the medulla oblongata and the pons found in premature infants dying shortly after birth and the importance of these hemorrhages as an etiological factor in respiratory disorders in newborn premature infants. The material for the study consisted of 51 liveborn premature infants dying within 30 days after birth and 3 stillborn premature infants, and of a control series of 14 liveborn fullterm infants dying within the same period and 6 stillborn fullterm infants. About one-fourth of all the liveborn children, both premature and fullterm, died within the first 2 hours *post partum*, about one-half within the first 24 hours, and a full four-fifths within the first week of life. Clinical observations were conducted in all cases, particular attention being paid to disorders in respiration. In addition to complete autopsy, histologic examination for hemorrhage was made of the medulla oblongata and the pons. An average of about 40 microscopic sections was made from the medulla and the pons in each case, mostly from the medullary region. In twelve cases the region of the quadrigeminal bodies was also subjected to microscopic examination.

In the premature infant series, microscopic hemorrhage in the medulla oblongata (in the medullary tissue or in the fourth ventricle) was encountered in 20/54 cases<sup>1)</sup> (37 per cent). In eleven cases the hemorrhage was situated in the actual medullary tissue, and in six of these its localization within the area of the respiratory center was regarded as probable. In fourteen cases

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<sup>1)</sup> Read: 20 out of 54 cases.

hemorrhage was present in the fourth ventricle. In five cases this finding was simultaneous with the finding of microscopic hemorrhage in the medullary tissue. Microscopic hemorrhage in the medulla oblongata without coincident macroscopic intracranial hemorrhage was encountered in ten cases (18 per cent). Altogether the findings of hemorrhage at postmortem examination were macroscopic intracranial hemorrhage (25 cases) and only microscopically seen medullary hemorrhage (10 cases) in a total of 35/54 cases, or in 65 per cent of the total series of premature infants examined. No variance was found in the incidence of microscopic hemorrhages of the medulla according to the weight of the children at birth. Grouped according to the age of the infants, microscopic hemorrhage in the actual medullary tissue was only present in stillborn premature infants or those dying within three days, and in the fourth ventricle in stillborn cases or deaths within eight days. The incidence of microscopic medullary hemorrhage was not influenced by the presentation of the child, operative intervention at delivery, tentorial laceration, age or parity of the mother, or maternal nephropathy or syphilis.

*Microscopic hemorrhage in the pons* was encountered in premature infants simultaneously with microscopic hemorrhage in the medulla oblongata in eight cases and without such medullary hemorrhage in one case, or in a total of 9/52 cases (17 per cent). The hemorrhages present in both the medulla and the pons were small in size and had their origin in either the capillaries or the small veins. A part at least of the hemorrhages encountered in the fourth ventricle had their source in the network of the choroid plexus. Microscopic examination made in ten cases in the region of the quadrigeminal bodies revealed no bleeding.

In the series of fullterm infants, *microscopic hemorrhage of the medulla oblongata* was encountered in 10/20 cases (50 per cent). In seven cases it was situated in the actual medullary tissue, and in three of these its location within the area of the respiratory center was regarded as probable. Hemorrhage was present in the fourth ventricle in seven cases, being in four of them simultaneous with a medullary tissue hemorrhage. Microscopic hemorrhage of the medulla oblongata was only present in

the stillborn infants or those dying within the first three days. Macroscopic intracranial hemorrhages (13 cases) and only microscopically visible medullary hemorrhages (4 cases) were seen in a total of 17 cases (80 per cent) in the series of fullterm infants. In the pons, microscopic hemorrhage was present in three cases coincidently with such hemorrhage in the medulla. No microscopic hemorrhage was found in the region of the quadrigeminal bodies in the two cases examined. No essential differences between fullterm and premature infants were seen in the character and localization of the microscopic hemorrhages of the medulla and the pons. In association with tentorial laceration microscopic medullary hemorrhage was present in fullterm infants in 3/3 cases. Fullterm infants showed a higher incidence of both microscopic hemorrhage of the medulla and macroscopic intracranial hemorrhage than premature infants, whereas the incidence of microscopic hemorrhage of the pons was approximately equal in fullterm and premature infants. Foci of softening were not seen in association with medullary and pons hemorrhages in either series of infants.

Distinctly observable *respiratory disorders* were present in the premature infant series in 39/51 cases (76 per cent). In association with such disorders microscopic medullary hemorrhages were encountered in 15/39 cases (38 per cent). It was regarded as probable that in 5/39 cases the hemorrhage was localized within the area of the respiratory center. No differences according to the localization of these hemorrhages could be observed in the character of the respiratory disorders. In premature infants born in an asphyctic condition and suffering from respiratory disorders a higher incidence of microscopic hemorrhages of the medulla oblongata was seen (5/10 cases, 50 per cent) than in those born in a live condition and likewise suffering from these disorders (10/29 cases, 34 per cent).

Microscopic hemorrhage was encountered in the pons in the case of 7/37 premature infants with respiratory disorders; in six cases it was present simultaneously with medullary hemorrhage. Macroscopic intracranial hemorrhage was encountered in connection with respiratory disorders in premature infants in 19/39

cases, or in 49 per cent; in five of these cases such hemorrhage was also present in the environment of the medulla. Pneumonia or pulmonary atelectasis was present simultaneously with respiratory disorders in 25/39 cases, or in 64 per cent.

Simultaneously with microscopic hemorrhage of the medulla oblongata (15 cases), the premature infants in whom respiratory disorders were observed were found to have macroscopic intracranial hemorrhage (3 cases), macroscopic intracranial hemorrhage and pulmonary changes (5 cases), pulmonary changes only (3 cases), or no macroscopically visible pathological changes (4 cases). Microscopic medullary hemorrhage was the sole pathological finding in only one of the premature infants suffering from respiratory disorders.

In 24/39 cases, or in 62 per cent, no microscopic medullary hemorrhage was found in premature infants suffering from respiratory disorders. Autopsy findings in these cases were macroscopic intracranial hemorrhage (3 cases), macroscopic intracranial hemorrhage and pulmonary changes (8 cases), pulmonary changes only (9 cases), or no macroscopic pathologic changes (4 cases).

*It is thus seen that the respiratory disorders observed in the premature infants were not strictly confined to any given pathologic change recognized.* It was, however, possible to note a slightly higher incidence of microscopic hemorrhage of both the medulla oblongata and the pons as well as of macroscopic intracranial hemorrhage and pulmonary changes in premature infants with respiratory disorders than in cases where such disorders were not observed. With but one exception, the medullary hemorrhages situated within the probable area of the respiratory center (6) were only encountered in premature infants suffering from respiratory disorders. Most cases of disorder furthermore showed a higher capillary blood content in the medulla and the pons than those in which disorders were not observed. On the other hand, macroscopic intracranial hemorrhage, microscopic hemorrhage of the medulla or the pons, and pulmonary changes were encountered in some premature infant cases without a clinical finding of

respiratory disorders. However, no macroscopic hemorrhage in the environment of the medulla oblongata was seen in these cases.

In fullterm infants respiratory disorders were observed in 11/14 cases (78 per cent). The pathologic changes found in association with such disorders were similar in nature to those made in the premature infants.

*As a summarizing observation it can be said that even if microscopic hemorrhages of the medulla oblongata and the pons are fairly common in cases of neonatal death of premature infants they usually are small in size and seem to have no decisive importance in the causation of respiratory disorders in premature infants. On the other hand, these hemorrhages are a manifestation of injury to tissue in the region of the respiratory center, and such injury apparently has a harmful effect upon the respiratory function. A number of other factors external to both the medulla oblongata and the pons participate in the control of respiration, and in the majority of cases of respiratory disorders in premature infants there simultaneously may be observed several etiologic factors which conjointly may lead to the occurrence of such disorders.*

Case No.; Hospital Report No.	Age of Child; Weight at Birth;	Age of Mother; Parity	Complications at Delivery	Postpartum Condition of Child	Later Condition of Child	Findings at Autopsy	Microscopic Findings		
							Hemorrhage in Medulla Oblongata	Hemorrhage in Pons	
38 519/I/46/N A-child	13 ½ hrs. 1,310 g. footling	36 yrs. VI-paro	Triple pregnancy; A-child; internal podalic version and extraction	Lively	At first lively, later cyanotic, restless, complaining. Constant administration of oxygen. Occasional attacks of weakness, with child still and apparently lifeless	Mild leptomeningeal edema (skull only opened)	In fourth ventricle	—	
62 1184/41/E	14 hrs. 1,700 g. vertex	40 yrs. III-paro	—	Lively	Cyanosis, difficult respiration; complains at each breath. Constant administration of oxygen	edema; coagulum lateral to medullæ; blood in ventricles; Atel. pulm.	Within and in floor of fourth ventricle	—	
63 1391/41/E	5 days 1,100 g. vertex	33 yrs. I-paro	—	Lively	At first lively; starting with 3rd day, respiration irregular; occasionally cyanosed, somnolent. In the end cessations of respiration	Leptomeningeal edema	In fourth ventricle	—	
89/46 2439/46/L	8 days 2,400 g. vertex	25 yrs. I-paro	—	Lively	On 1st day grayish, cyanotic; respiration irregular and interrupted; resuscitates in oxygen couveuse. Occasional inspiratory difficulties	Heavy leptomeningeal edema; Atel. pulm.; Pneum. I. dx.	In wall of fourth ventricle	—	
104/46 2542/46/L	11 hrs. 1,350 g. Cesarean section	36 yrs. I-paro uterine myoma	Intrauterine asphyxia; couveuse; repeated attacks of cyanosis	Lively	Subnormal temperature; cyanosed; difficult respiration, especially inspi- ration; kept in oxygen	Subpial hemorrhage in occipital region	—	(No micro- scopic examination made)	

## PRINCIPAL CLINICAL OBSERVATIONS AND PATHOLOGIC FINDINGS IN PREMATURE AND FULLTERM INFANTS

TABLE X<sup>1</sup>

## a. Premature infants suffering from respiratory disorders and with microscopic hemorrhage of the medulla oblongata

Case No.; Hospital Report No.	Age of Child; Weight at Birth; Presentation	Age of Mother; Parity	Complications at Delivery	Postpartum Condition of Child	Later Condition of Child	Findings at Autopsy	Microscopic Findings		
							Hemorrhage in Medulla Oblongata	Hemorrhage in Pons	
6 294/I/39/N	25 hrs. 2,020 g. vertex	27 yrs. II-paro	Placenta praevia marginalis	Lively	Interruptions of respiration; cyanosis. Constant administration of oxygen	Leptomeningeal edema; Atel. pulm.	Under floor of 4th ventricle and in hilus of interior olive	—	
19 705/IV/39/N	5 ds. 2,270 g. vertex	32 yrs. I-paro	Maternal syphilis	Slightly asphyxiated	Constant cyanosis; on last days respiration poor and superficial	Heavy leptomeningeal edema; blood coagula in fourth ventricle; Pneum. l. dx.	Blood in 4th ventricle; blood cells partly decomposed	In wall of fourth ventricle	
28 785/I/39/N	Agonal 2,460 g. footling	23 yrs. I-paro	Maternal nephropathy	Deeply asphyxiated	Some weak respiratory movements; did not resuscitate	Leptomeningeal edema; bilateral tentorial laceration; small amount of uncloated blood in basal part; Atel. pulm.; Hydrops univ.	Under floor of 4th ventricle	In wall of fourth ventricle at margin of medulla and pons	
36 519/II/46/N C-child	29 hrs. 1,080 g. footling	36 yrs. VI-paro	Triple pregnancy; C-child; extraction	At first lively, color good, respiration good; 2 hrs. before death became cyanotic, complaining; respiration poor	Heavy leptomeningeal edema; Medulla surrounded by thick coagulum; blood in cerebral ventricles; lungs air-filled, with exception of paravertebral areas	Blood in 4th ventricle; leptomeninges show extensive hemorrhages, decomposing blood cells	—		

EXPLANATIONS OF LETTERS IN HOSPITAL REPORT Nos.: N = Women's Clinic of the University of Helsinki; L = Children's Clinic of the University of Helsinki; E = Helsinki Municipal Epidemic Hospital; K = Midwives' College, Helsinki.

22/47 497/47/L	7 days 1,670 g. vertex	21 yrs. I-para	—	Lively	At first cyanotic, later quite lively; on 4th day tired, pale, respiration uneven, irregular, superficial; kept in oxygen couveuse; later cramps, cyanosis, gasping respiration	Leptomeningeal edema; extensive hemorrhage in leptomeninges in temporal and occipital regions; punctate hemorrhages in environment of left lateral ventricle	In fourth ventricle	—
33/47 559/47/L	5 days 1,380 g. vertex	23 yrs. I-para	—	Lively	Respiration occasionally poor, short, superficial; cyanotic attacks; kept in oxygen couveuse	Heavy leptomeningeal edema; Atel. pulm.	In fourth ventricle	—
102 586/39/K	24 hrs. 2,160 g. breach-footing	34 yrs. I-para	Extraction of breech-footing; presentation; oblique pelvis	Deeply asphyxiated	Respiration irregular, uneven; cessations of respiration, cyanosis	Mild leptomeningeal edema; tentorial laceration on right side; hemorrhage on convexity and basal part; also around medulla	In margin of inferior olive	In lateral part
203 459/39/K	40 hrs. 1,730 g. vertex	26 yrs. I-para	—	Lively	Asphyctic attacks; cyanosis; spasms in extremities. Dies during an asphyctic attack	Leptomeninges edematous and blood-filled	Blood in 4th ventricle; small effusion fourth of blood in roof of 4th ventricle and in region of raphe dorsal to olive	In wall of
206 744/L/39/N	24 ½ hrs. 780 g. vertex	34 yrs. IV-para	—	Deeply asphyxiated	Respiration irregular, Cheyne-Stokes type. Dies as cyanosis increases and respiration becomes superficial.	Leptomeningeal edema; abundant hemorrhage around cerebellum and medulla; ventricles blood-filled; Atel. pulm.	In fourth ventricle and leptomeninges	In leptomeninges
39 531/II/46/N	3 hrs. 1,560 g. breach	27 yrs. II-para	—	Deeply asphyxiated	Cyanotic; color occasionally better; respiration fairly good	Leptomeningeal edema; mucus in trachea and bronchi	Subpial	—

b. Premature infants with microscopic hemorrhage of the medulla oblongata in whom no respiratory disorders were observed.

Case No.; Hospital Report No.	Age of Child; Weight at Birth; Presentation	Age of Mother; Parity	Complications at Delivery	Postpartum Condition of Child	Later Condition of Child	Findings at Autopsy		Microscopic Findings Hemorrhage in Medulla Oblongata
1 161/II/39/N	4 days 995 g. breech	32 yrs. I-paro	—	Lively	Cyanotic; condition gradually worsens	Abundant leptomeningeal hemorrhages on both hemispheres and in environment of cerebellum; blood in cerebral ventricles; blood in spinal canal	In fourth ventricle	Subpial
16 576/II/39/N	2 hrs. 1,100 g. footling	28 yrs. IV-paro	—	Lively	Weakened gradually	Leptomeningeal edema; Atel. pulm.	In. fourth ventricle	—
30 923/II/39/N	2 days. 870 g. vertex	23 yrs. II-paro	—	Lively	Cried lustily after birth; weakened gradually	Heavy leptomeningeal edema	Around olive	In roof of fourth ventricle
111 1069/39/K	1 hr. 50 m. 570 g. vertex	28 yrs. I-paro	Twin pregnancy; B-child	Lively	Cried; respiration fairly good	Leptomeningeal edema; Atel. pulm.	In fourth ventricle	—

c. Premature infants suffering from respiratory disorders but with no microscopic hemorrhage of the medulla oblongata.

IV 218/39/L	20 hrs. 1,800 g. vertex	?	Maternal pneumonia; I-paro forceps	Slightly asphyxiated	Respiration poor; when oxygen mask momentarily removed, child becomes deeply cyanosed	Extensive hematoma on left hemisphere; Atel. pulm.	—	—
3 1069/39/K	24 hrs. 1,800 g. vertex	Agonal	—	—	—	Efforts to resuscitate un- conscious	Deeply cyanosed	Laceration of falx; blood

3 166 I/39/N	Agonal 24 yrs. I-para 1,450 g. breach	—	Deeply asphyxiated	Efforts to resuscitate un- successful; died 20 min. after birth	Laceration of falx; blood in subdural cavity, cere- brospinal fluid blood- tinged; Atel. pulm.
7 363 II/39/N	Agonal 22 yrs. I-para 920 g. breach- footling	—	Agonal	A few respirations and utterances	Leptomeningeal edema; effusions of blood in lepto- meninges; Atel. pulm.; hepatic laceration, hemor- rhage into abdominal cavity
10 394 II/39/N	1 hr. 50 m. 1,270 g. vertex	19 yrs. I-para	Lively	At first lively, then ces- sations of respiration	Leptomeningeal edema; blood in lateral ventricle; cerebrospinal fluid in spinal canal blood-tinted
11 394 I/39/N	Agonal 870 g. vertex	27 yrs. I-para	Agonal	Two or three superficial breaths after birth; did not cry. No artificial re- spiration or insufflation	Leptomeningeal edema; Atel. pulm.
13 415 I/39/N	1 hr. 20 m. 1,845 g. vertex	41 yrs. IX-para Hydranion	Lively	At first lively; later cya- nosis, difficult respiration; complained at each breath	Heavy leptomeningeal edema; Atel. pulm.
20 737 I/39/N	3 hrs. 1,590 g. vertex	26 yrs. II-para	Lively	At first lively; cried; re- spiration ordinary. 2 hrs. later condition suddenly weakens; respiration gasp- ing (Schnappatmung) until end	Heavy leptomeningeal edema; left territorial laceration; Atel. pulm.
37 518 II/46/N B-child	14 hrs. 1,180 g. footling	36 yrs. VI-para	Triple preg- nancy; B-child; extraction	Mild leptomeningeal edema; lungs air-filled, with exception of para- vertebral areas	At first lively, later cya- notic, restless, complain- ing; occasional cessations of respiration

Case No.; Hospital Report No.	Age of Child; Weight at Birth; Presentation	Age of Mother; Parity	Complications at Delivery	Postpartum Condition of Child	Later Condition of Child	Microscopic Findings		
						Findings at Autopsy	Hemorrhage in Medulla Oblongata	Hemorrhage in Pons
64 958/46/E	5 days 1,720 g. vertex	21 yrs. I-para	—	Lively	At first lively; 2 days later cyanosis, rhinitis; difficult inspiration; respiration rapid, superficial, irregular	Leptomeninges blood-filled; brain matter abnormally blood-filled	—	—
65 835/46/E	21 hrs. 1,730 g. vertex	24 yrs. I-para	—	Lively	Respiration poor, irregular, grunting; rate 70—200 per min.; cyanosis	Left tentorial laceration; effusions of blood in tentorium; Atel pulm.	—	Under floor of fourth ventricle
66 635/46/E	24 days 2,000 g. vertex	38 yrs. III-para	—	Lively	At first lively; 2 wks. later rhinitis, pulmonary rale, respiration difficult and panting; diarrhea	Pneum. I.a.; Enteritis; Icterus	—	—
67 409/46/E	11 days 2,240 g. breech	19 yrs. I-para	Maternal syphilis	Lively	At first lively; on last days rhinitis, respiration superficial and irregular. Congenital syphilis	Pneum. I.a.; mild leptomeningeal edema	—	—
103 584/39/K	14 days 1,010 g. breech	24 yrs. III-para	Maternal syphilis	Slightly asphyxiated	Respiration irregular, superficial, rate 20—40 per min.; in the end definitely gasping type (Schnappatmung)	Leptomeningeal edema; blood coagulum in vicinity of falx and upon corpus callosum; small amount of blood in both lateral ventricles	—	—
108 833/39/K	2 hrs. 40 m. 830 g. vertex	19 yrs. I-para	Delivery at home; child attached to placenta on hospitalization	Lively	Cyanosis; respiration irregular, occasionally of Cheyne-Stokes type	Leptomeningeal edema	—	—
								Respiration irregular; occ. Heavy leptomeningeal
								Lively
								4 days
								?

202 326/39/L	4 days 1,070 g. ?	?	—	Lively	Respiration irregular; occasional gasping attacks (Schnappatmung) and Cheyne-Stokes respiration	Heavy leptomeningeal edema
207 503/39/L	19 days 1,365 g. vertex	22 yrs. I-para	Mild maternal nephropathy	Lively	At first lively; respiration occasionally poor; attacks of cyanosis; on last days respiration irregular	Mild leptomeningeal edema; air content of basal lobe of both lungs somewhat reduced
93/46 2418/46/L	18 hrs. 1,500 g. vertex	30 yrs. IV-para	—	Lively	Upon hospitalization at age of 6 hrs. deeply cyanosed and respiration interrupted; resuscitated with oxygen; recurrent aphycic attacks	Blood coagulum on convexity of cerebrum; coagula on inferior surface of cerebellum and lateral medulla; blood in left lateral ventricle; Atel. pulm.
94/46 2443/46/L	7 hrs. 930 g. footling	38 yrs. II-para	Twin pregnancy; B-child	Lively	Grayish pale cyanotic hue; respiratory movements weak and uneven, occasionally absent	Leptomeningeal edema; Atel. pulm.
95/46 2442/46/L	8 hrs. 920 g. vertex	38 yrs. II-para	Twin pregnancy; A-child	Lively	Cyanotic, respiration very superficial, sometimes barely visible	Leptomeningeal edema
97/46 2444/46/L	4 days 1,940 g. vertex	31 yrs. II-para	Fast delivery (2 hrs.)	Lively	Restless, cyanotic, complaining; respiration superficial, with occasional cessations	Leptomeningeal edema; Atel. pulm.; (microscopic finding: Bronchopneum. I.a.)
109/46 2514/46/L	18 days 1,620 g. Cesarean section	32 yrs. I-para	Maternal nephropathy; eclampsia	Lively	Fairly lively for about a week, then respiration irregular and occasionally gasping (Schnappatmung)	Hemorrhage on upper surface of occipital lobe and in basal part; Pneum. I. sin.; Enteritis

Case No.; Hospital Report No.	Age of Child; Weight at Birth; Presentation	Age of Mother; Parity	Complications at Delivery	Postpartum Condition of Child	Later Condition of Child	Microscopic Findings	
						Findings at Autopsy	Hemorrhage in Medulla Oblongata
15.47 208/47/L	18 days 2,370 g. vertex	?	III-para	Lively	At first lively, weight gradually declines. In the end cyanosis; respiration uneven	Mild leptomeningeal edema; no macroscopicaly seen pneumonic foci; (microsc.: distinct pneumonic changes in lungs)	—
19.47 278/47/L	16 days 1,980 g. ?	Born on way to hospital	1-para	Lively	Subnormal temperature; respiration difficult and panting. Resuscitates temporarily; respiration later uneven; sometimes gasps deeply	Left tentorial laceration; leptomeningeal hemorrhage in occipital region; Meningitis	—
30.47 569/47/L	2 days 2,010 g. vertex	23 yrs.	Twin pregnancy; B-child	Lively	Limp, cyanosed, complaining. At age of 2 days has sudden attack of cyanosis; respiration ceases. Does not resuscitate	Bilateral tentorial laceration; subdural hemorrhage on cerebral convexity; Atel. pulm.	—

d. Premature infants in whom no respiratory disorders or microscopic hemorrhage of the medulla oblongata were observed

II 51/39/L	27 days 1,500 g. ?	IV-para	Delivery at home; details not known	Lively	In fair condition at first; gradually wastes away	Extensive hemorrhage on cerebral convexity	—
14 451/II/39/N	20 min. 610 g. breech	25 yrs. II-para	—	Lively	Fairly lively but slightly cyanosed post partum. Respiration gradually becomes poor	Leptomeningeal edema; effusions of blood in leptomeninges in parietal region; Atel. pulm.	—

21 708/1/39/N	40 min. 1,000 g. breach-footing	24 yrs. I-paro	—	Lively	Cyanotic; gradually becomes worse	Leptomeningeal edema; bilateral tentorial laceration; cerebrospinal fluid in spinal canal blood-tinted; Atel. pulm.
25 786/1/39/N	40 min. 1,050 g. breach	31 yrs. IV-paro	—	Lively	Cried aloud, cyanosed. Respiration gradually became poor as cyanosis increased	Leptomeningeal edema; Atel. pulm.
34 616/1/39/N	1 hr. 50 m. 1,070 g. vertex	18 yrs. I-paro	—	Lively	Gradually weakens	Leptomeningeal edema
105 736/39/K	16 hrs. 2,060 g. vertex	20 yrs. I-paro	—	Lively	Cyanotic, restless, complaining; no interruptions of respiration. Sudden worsening and exitus	Leptomeningeal edema; Atel. pulm.
110 1069/39/K	1 hr. 30 m. 950 g. vertex	28 yrs. Twin pregnancy; A-child	—	Lively	At first lively, cried; respiration fairly good	Leptomeningeal edema; effusions of blood in leptomeninges on convexity; Atel. pulm.
204 475/39/L	6 days 1,640 g. vertex	21 yrs. I-paro	—	Lively	Temperature rises, cyanosis, abdomen swollen	Leptomeningeal edema

e. Stillborn premature infants

Case No.; Hospital Report No.	Age of Child; Weight at Birth; Presentation	Age of Mother; Parity	Complications at Delivery	Postpartum Condition of Child	Later Condition of Child	Findings at Autopsy		Microscopic Findings Hemorrhage in Medulla Oblongata	Hemorrhage in Pons
8 368/L/39/N	— 2.270 g. vertex	— 22 yrs. I-paro	Umbilical cord twice around neck	Stillborn	Died during delivery	Leptomeningeal edema; Atel. pulm.	—	—	—
9 380/L/39/N	— 1,380 g. breech	— 21 yrs. I-paro	Ablation plac. ante tempus	Stillborn	—	A few blood coagula at cerebral base; cerebro-spinal fluid in spinal canal blood-tinted; Atel. pulm.	In fourth ventricle and olive	—	—
22 708/L/39/N	— 990 g. breech-footing	— 24 yrs. I-paro	Twin pregnancy; B-child	Stillborn	Died during delivery	Leptomeningeal edema; Atel. pulm.	—	—	—

f. Fullterm infants suffering from respiratory disorders and with microscopic hemorrhage of the medulla oblongata

27 815/L/39/N	Agonal 3,380 g. brow	29 yrs.	Albuminuria; Deeply asphyxiated	Bilateral tentorial laceration; laceration of fat; subdural hemorrhage; cerebrospinal fluid blood-tinted; Atel. pulm.
29 879/L/39/N	2 days 2,800 g. vertex	24 yrs. I-paro	—	At first limp, transiently lively. Recurrent asphyctic attacks
31	Agonal	30 yrs.	Twin preg-	Lively
				Bilateral tentorial laceration; In roof of fourth ventricle

31 936/II/39/N	Agonal 2,770 g. vertex	30 yrs. Twin preg- nancy; B-child	Deeply asphyxiated	Deeply asphyxiated at birth; could not be resuscitated
32 932/II/39/N	Agonal 2,890 g. face	23 yrs. Face I-para presentation	Deeply asphyxiated	Postpartum condition poor; could not be resuscitated
106 750/39/K	50 min. 3,000 g. vertex	26 yrs. III-para	Lively	At first lively, cried; 6—7 min. later respiration suddenly ceased but heart action continued; 30 min. inflation.
107 760/39/K	7 hrs. 3,250 g. vertex	32 yrs. II-para	Deeply asphyxiated	Pale, limp; respiration slow and interrupted. Much mucus in trachea
		Mother imbecil.		Leptomeningeal edema; extensive subdural hematoma on cerebral convexity; unclotted blood in left pleural cavity

g. Fullterm infants with microscopic hemorrhage of the medulla oblongata in whom no respiratory disorders were observed.

				Atel. pulm.; Icterus	Severely icteric	In olive and vicinity of central canal	In wall of fourth ventricle
4 235/I/39/N		2 days 2,960 g. vertex	25 yrs. II-para	—	Lively		

*h. Fullterm infants suffering from respiratory disorders but with no microscopic hemorrhage of the medulla oblongata*

Case No.; Hospital Report No.	Age of Child; Weight at Birth; Presentation	Age of Mother; Parity	Complications at Delivery	Postpartum Condition of Child	Later Condition of Child	Findings at Autopsy		Microscopic Findings	
						Hemorrhage in Medulla Oblongata	Hemorrhage in Pons		
III 181/39/L	2 days 4,450 g. vertex	30 yrs. III-para	Umbilical cord twice around neck	Lively	At first lively later hemorrhages in different parts of body; respiration difficult and panting	Extensive subdural hemorrhage; hepatic laceration; hemorrhage into abdominal cavity	—	—	—
205 480/39/L	14 days 3,500 g. vertex	? IV-para	—	Lively	Tired on last two days; breathing frequently increased. Nostril respiration; attacks of cyanosis	Leptomeningeal edema; Pneum. l.sin.	—	—	—
5 244/II/39/N	3 days 2,980 g. vertex	29 yrs. I-para	Umbilical cord twice around neck	Slightly asphyxiated	At first respiration poor; child transiently lively. Convulsions on last day	Hemorrhage in environment of left lateral ventricle	Some isolated blood cells outside greatly enlarged capillaries; no actual hemorrhage	—	—
104 535/39/KS	16 days 3,030 g. vertex	? ?	Maternal nephropathy; asphyxia of child; forceps	Slightly asphyxiated	At first cyanosis, respiration difficult. On last days rhinitis and asphytic attacks	Leptomeningeal edema; effusions of blood on cerebral convexity and at cerebral base	—	—	—
68/47 689/II/47/N	4 hrs. 3,220 g. vertex	27 yrs. II-para	—	Lively	Limp, cyanotic, panting, respiration difficult; nostril respiration	Hemorrhage at cerebral base; intestinal hemorrhage; left kidney missing	—	—	—

i. Fullterm infants in whom no respiratory disorders or microscopic hemorrhage of the medulla oblongata were observed

Case No.; Hospital Report No.	Age of Child; Weight at Birth; Presentation	Age of Mother; Parity	Complications at Delivery	Postpartum Condition of Child	Later Condition of Child	Findings at Autopsy		
						Hemorrhage in Medulla Oblongata	Hemorrhage in Pons	Microscopic Findings
24 773/I/39/N	2 days 4,250 g. vertex	31 yrs. II-para	Duration of delivery 2 hrs.	Lively	At first cyanosis; condition improves later. In the end dark vomit, pallidness, rapid worsening	Extradural blood coagula in cerebrospinal canal; hemorrhage into pleural cavity, lung, liver, abdominal cavity, and suprarenal body	—	—
28 870/II/39/N	2 days 4,085 g. vertex	28 yrs. II-para	—	Lively	At first lively; on 2nd day diarrhea; progressing worsening of condition	Mild leptomeningeal edema; leptomeningeal effusions of blood on cerebral convexity; effusion into capsula interna; Enteritis	—	—

*j. Stillborn fullterm infants*

Case No.; Hospital Report No.	Age of Child; Weight at Birth; Presentation	Age of Mother; Parity	Complications at Delivery	Postpartum Condition of Child	Later Condition of Child	Findings at Autopsy			Microscopic Findings Hemorrhage in Medulla Oblongata	Hemorrhage in Pons
2 163/I/39/N	— 3,400 g. vertex	— 30 yrs. II-para	Flat pelvis; prolapse of umbilical cord	Stillborn	Died during delivery	Atel. pulm.		In floor of fourth ventricle	—	—
12 404/II/39/N	— 3,870 g. oblique	— 41 yrs. IX-para	Maternal nephropathy and syphilis. Prolapse of cord; internal podalic ver- sion and extraction	Stillborn	Died during delivery	Laceration of falx; blood coagula in environment of pons and medulla; Atel. pulm.		—	—	—
15 328/I/39/N	— 3,560 g. oblique	— 32 yrs. III-para	Twin preg- nancy; B-child, Hy- drocephalus; extraction	Stillborn	Died during delivery	Laceration of falx; un- clotted blood on floor of cranial cavity; cerebro- spinal fluid in spinal canal blood-tinted; Hydro- cephalus		—	—	—
17 675/I/39/N	— 4,180 g. vertex	— 33 yrs. III-para	—	Stillborn	Died during delivery	Leptomeningeal edema; slight effusion of blood at cerebral base (skull only opened)		—	—	—
23 785/II/39/N	— 3,745 g.	— 31 yrs. I-para	Asphyxia iii.	Stillborn	Died during delivery	Bilateral territorial lacer- ations		Pial and subpial	—	—

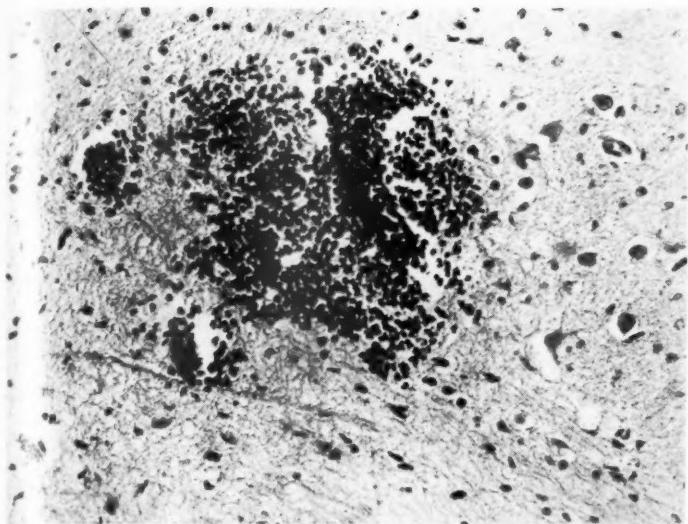
23	785/II/39/N	3,745 g. breech	—	31 yrs. I-paro I-u;	Asphyxia extraction	Stillborn	Died during delivery	Bilateral tentorial laceration; abundant coagulated and uncoagulated blood around cerebellum and medulla, blood in cerebral ventricles (skull only opened)	Pial and subpial; in fourth ventricle
33	595/I/39/N	3,450 g. vertex	—	26 yrs. I-paro I-u	Twin preg- nancy; A-child; Maternal nephropathy; Inertia uteri	Stillborn	—	Leptomeninges blood- filled; Atel. pulm.	—

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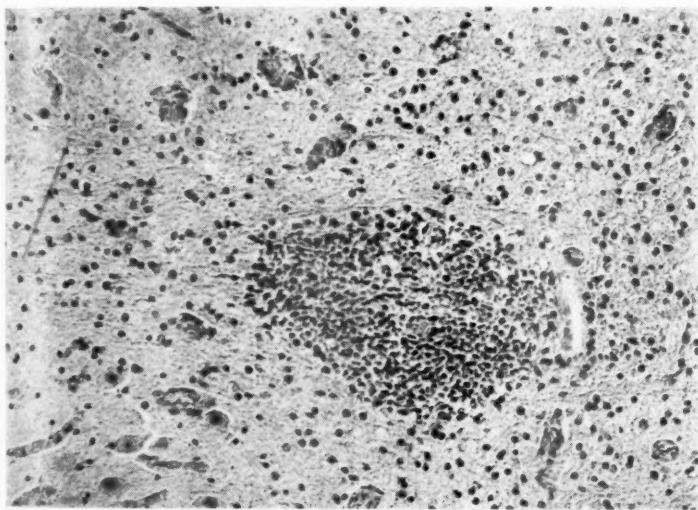
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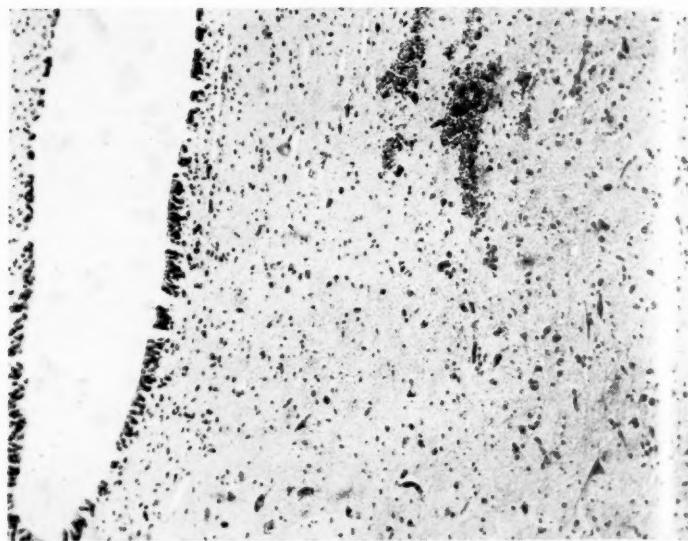
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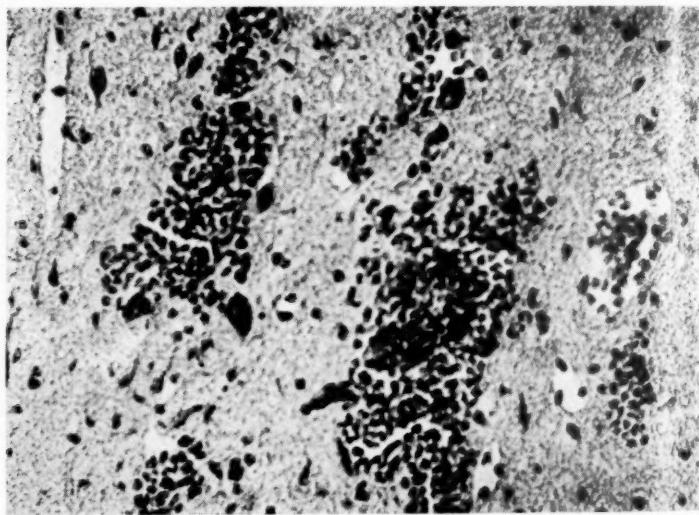
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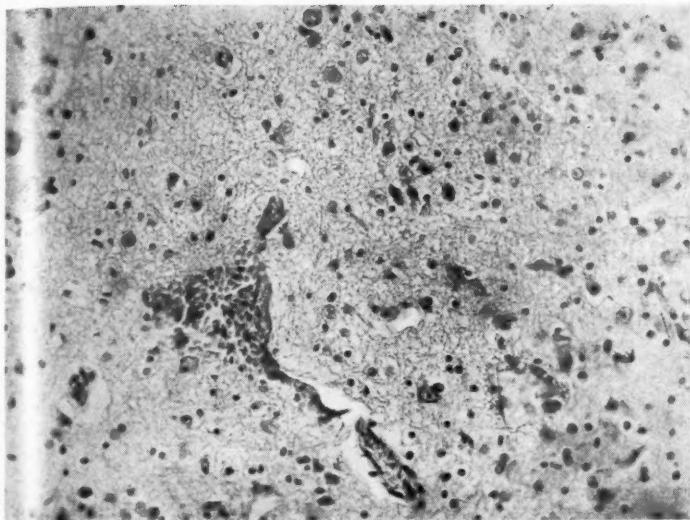
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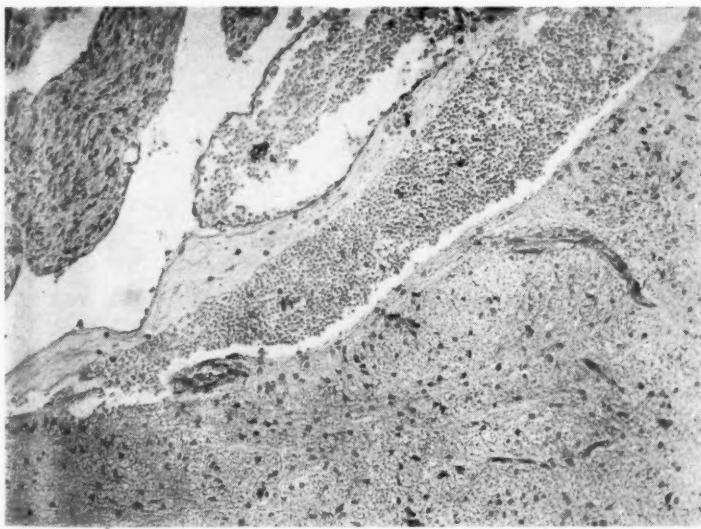
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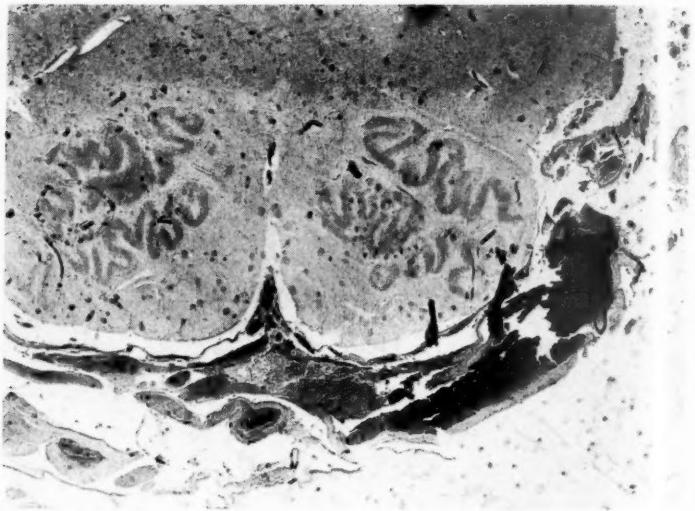
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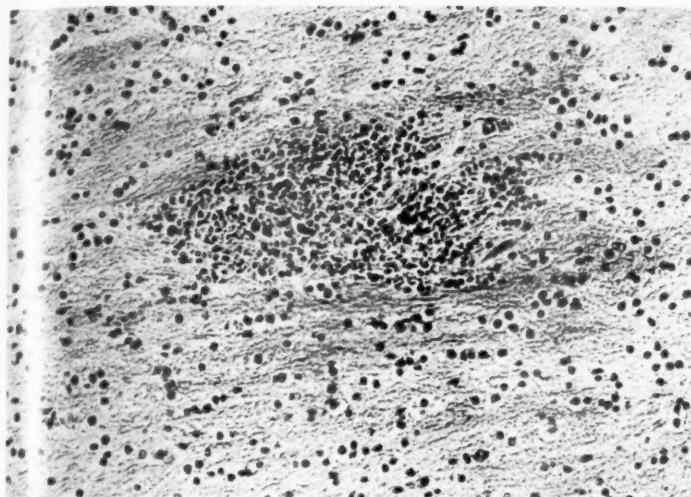
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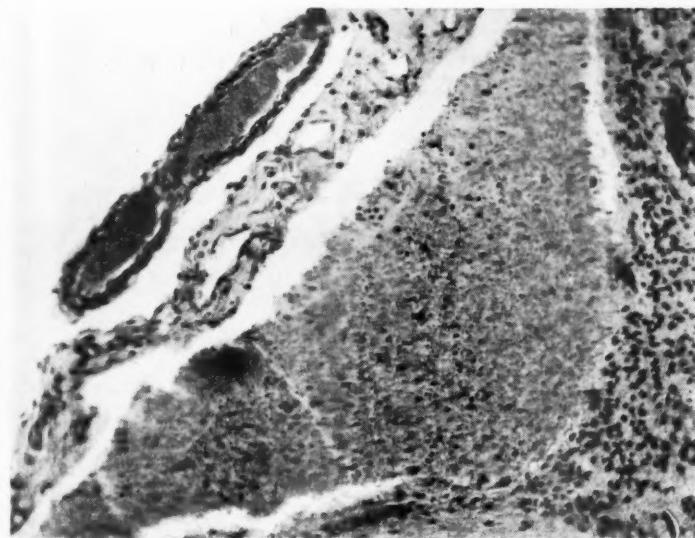
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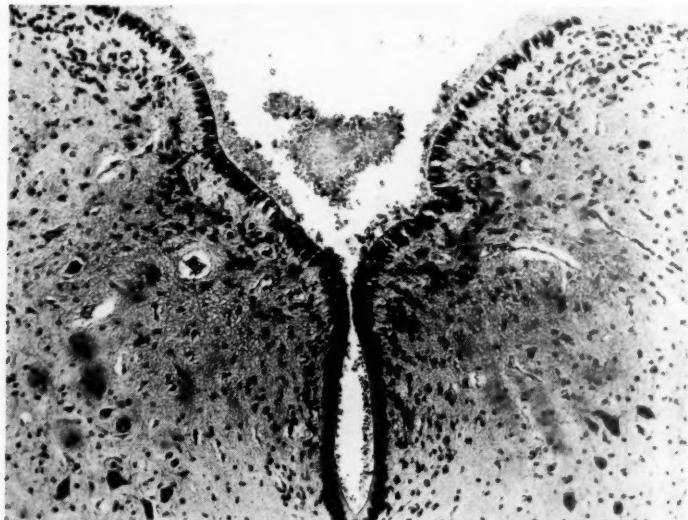
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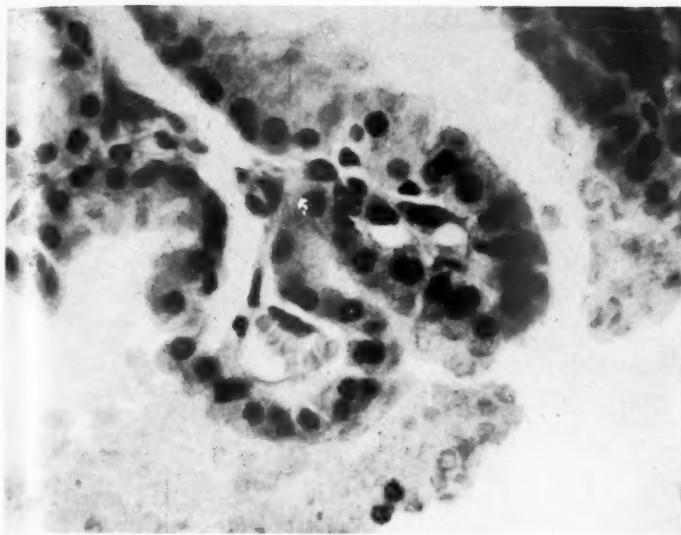
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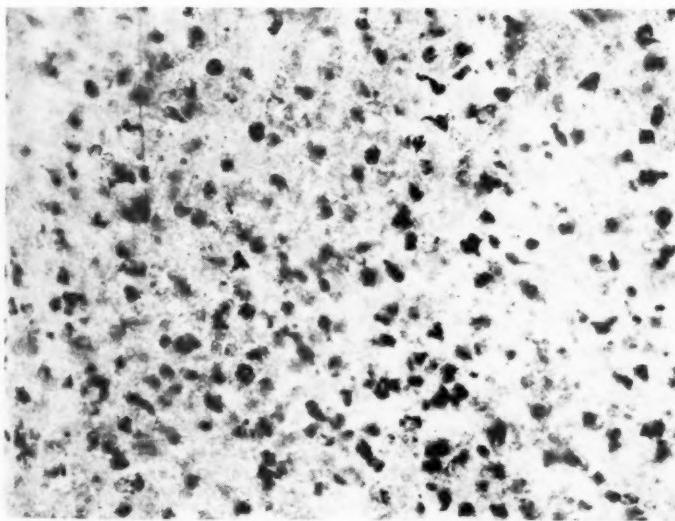
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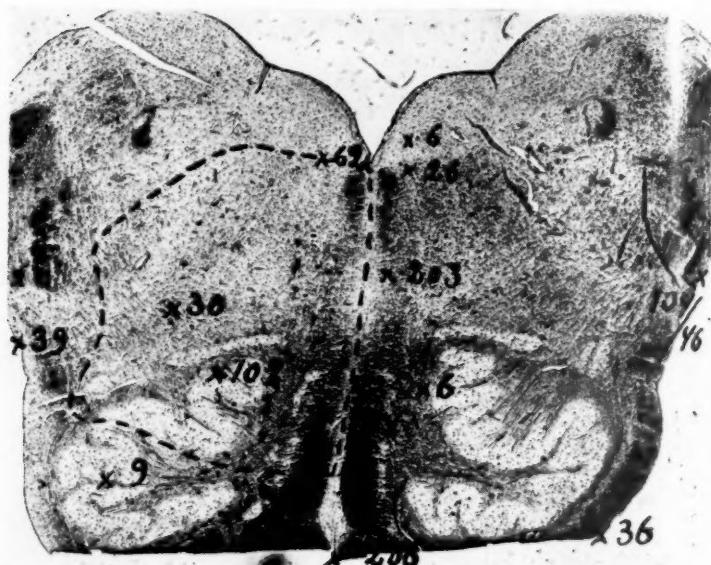
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From the Paediatric Clinic of the Caroline Institute at Norrtull's Hospital,  
Stockholm. Head: Prof. A. Wallgren

## RESPIRATORY INFECTIONS AMONG CHILDREN IN DAY NURSERIES

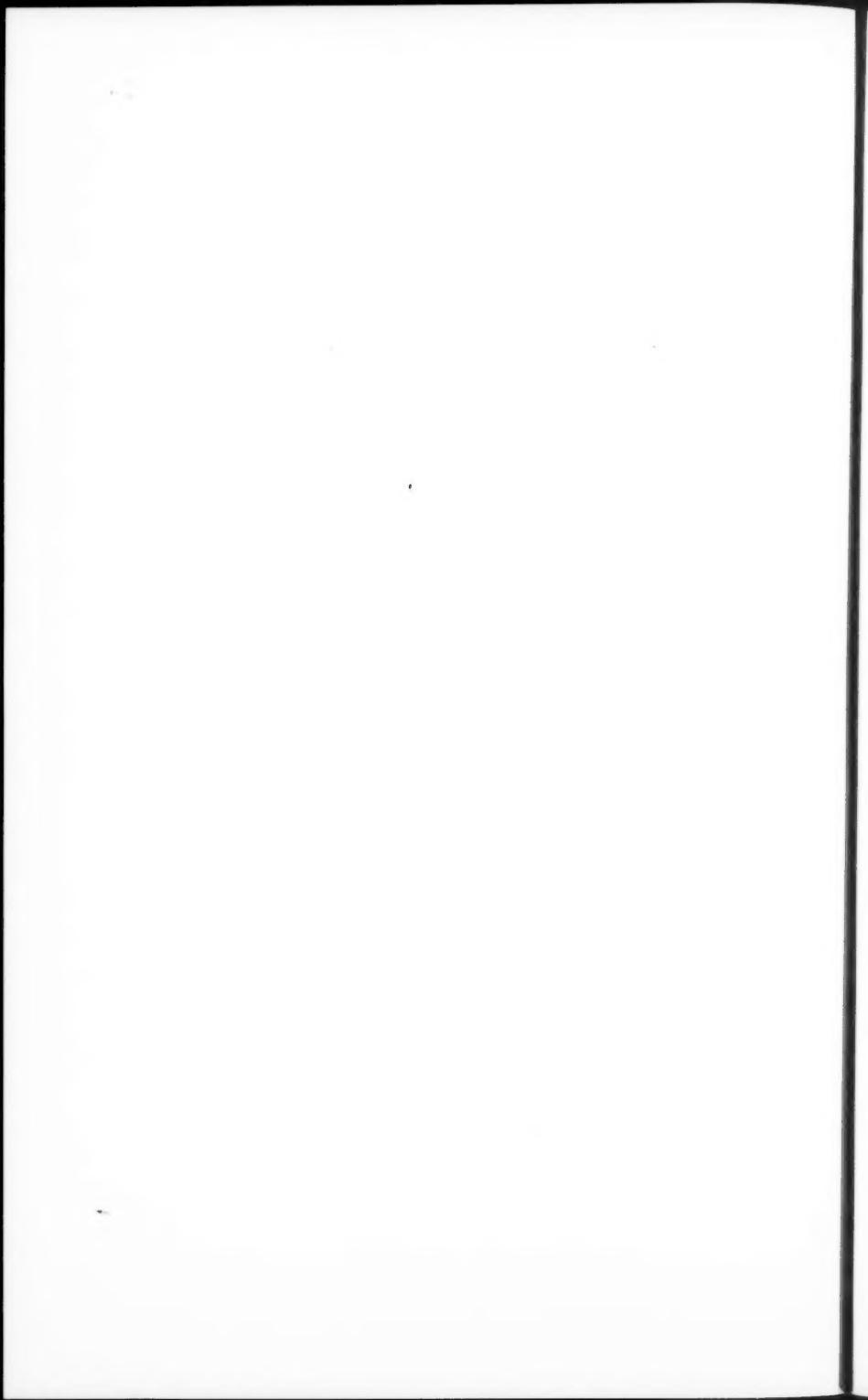
BY

LENNART HESSELVIK

ACTA PÆDIATRICA, SUPPLEMENTUM 74

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*Stockholm 1949*



*To my Parents*

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### Preface

The work presented here forms part of the investigations and experimental studies on the infection risks in pre-school institutions which have been planned and are being carried out under the auspices of the 1946 Committee for the rearing of children partly outside the home.

My interest in these problems was aroused by my chief, Professor Arvid Wallgren, and he gave me the opportunity, as a member of his staff at the Paediatric Clinic at Norrtull's Hospital, to go further into the question. For his courtesy in this respect, and for his great kindness in advising me in the light of his wide experience in medical research and social service, I am greatly indebted to him.

I also proffer my warmest thanks to the initiator of the above-mentioned investigations, Professor Gunnar Löfström. His ability to give skilful leadership, while at the same time allowing his colleagues opportunities for personal initiative and independent work, has been a constant source of inspiration. I am also very grateful to Dr Gunnel Melin, member of the same research team, for her agreeable co-operation, and to both E. N. T. specialists with whom I collaborated, Dr L.-E. Floberg and Dr G. Bjuggren.

I have received great assistance and courteous treatment from the public authorities, the State Social Board and the Child Welfare Board of the City of Stockholm, with which, during the course of the investigation, I had active contact. I would therefore like to extend my thanks to the officers concerned.

Ever since the first plan of the investigation was worked out over three years ago, I have had the advantage of almost daily contact with the statistician, Fil. lic. Stig W. Nilsson, and I take this opportunity of expressing my deep gratitude for his indefatigable work with the statistical analyses and the energy he has expended on my behalf.

Valuable suggestions in connection with certain statistical problems have been offered by Professor Carl-Erik Quensel,

Lund, Docent Leonard Goldberg and Amanuens Jan Jung, Stockholm, and their friendly advice on these matters is greatly appreciated.

I would also like to thank my colleagues at the Clinic for stimulating discussions and useful assistance.

During the whole course of this investigation I have had extremely valuable help from Miss Lillie Lundberg, in her capacity as health visitor. She has in a very helpful and loyal way assisted me both with practical work connected with the investigation and with secretarial work. Her attention to detail and indefatigability have been exemplary. For efficient help for shorter periods I would also like to thank Mrs Siv Backman, Mrs Stina Hallberg and Mrs Brita Thulin.

Mrs Grace Lundberg, B. A., and Miss Carol Maurice, B. A., S. R. N. have co-operated in the translation and I express my best thanks for their painstaking work.

Finally I proffer my grateful thanks to the staff of the day nurseries, for whom this investigation entailed much extra work, and to the large groups of parents whose willing and reliable co-operation made this study possible.

Stockholm, April 1949.

*Lennart Hesselvik*

## CHAPTER I

### *Introduction*

When a mother, usually through work outside the home, cannot look after her child during the day, a problem arises which society has tried to solve chiefly by establishing day nurseries. Here the mothers leave their children in the morning and fetch them again when the day's work is over. In earlier times, when women did not work outside the home so often, there was probably not a great need of such institutions. This need became more urgent with the emergence of industrialism in the 19th century.

The first day nursery in Sweden was opened in Stockholm in 1854. It came into being through the initiative of a physician, Magnus Huss, professor at the Caroline Institute (Wallgren 1945) and was in the nature of a public assistance institution for the worst situated members of society. During the next decades a number of such institutions were established, especially in the large towns. For a long time, however, the development was slow, doubtless because the nurseries were generally run by private societies with little or no support from public funds, and they often carried on under great economic difficulties. It was during the second World War that the number of Swedish nurseries began to increase to a considerable extent. In 1941 there were 156 institutions offering whole-day service to children. Of these, 87 were exclusively day nurseries, the others were combined with nursery schools and so on. (Report of the 1941 Population Committee, 1943). In 1948 the numbers had increased to 267 and 178 respectively, while the number of children who received nursery care increased from about 4,080 in 1941 to 10,150 in 1948.<sup>1</sup> This accelerated increase in the numbers of day nurseries was caused by the rapidly growing need for labour

<sup>1</sup> According to information from the Social Board.

which meant that women worked outside the home to a much greater extent than previously, and in conjunction with this the authorities became more aware of the significance of day nurseries. This interest is reflected in the fact that most nurseries at the present time have been taken over by the municipal authorities. Only a small proportion of day nurseries are now owned by private societies or industries, in the former case usually with municipal support. Since 1944, state contributions have been made to day nurseries on condition that they fulfill certain definite demands regarding the premises, qualifications of the staff, medical control of children and personnel, and other such details. All day nurseries at present must submit to inspection by a state authority, the Social Board.

All these measures have brought about a significant raising of the general standard of day nurseries during recent years. The institutions which are now being established are, generally speaking, of a very high standard. Another feature in the development of Swedish day nurseries during recent years might perhaps be worth mentioning. While the day nurseries are more and more losing their public assistance character, the increased difficulty of obtaining domestic help means that the day nursery clientele is at present recruited on a definitely broader social basis. While earlier it was only the children from the poorest homes who were admitted to day nurseries, to-day relatively well-to-do sections of the community are represented.

With this extension of day nursery activity, however, the problem of the children's health has come more into the foreground. These problems, which are of a mental as well as a physical type, can, in short, be said to originate from the fact that in a day nursery small children are gathered together in a small space for a large part of the day. Everyone would seem to be in agreement that day nurseries are unsuitable for infants; with few exceptions, infants require the mother's individual care. It is generally considered that young children, also, are little suited to collective care. They are individualists and, before three years old, are not, as a rule, capable of adjusting themselves to the demands of social behaviour, and it is therefore difficult to look after them in comparatively large groups. They irritate each other and tire each other out. It is just at this age that the problem of over-fatigue among day nursery children is most clearly seen. The period during which children are

away from home is long, often 9—10 hours a day, and they have little opportunity of being alone. Often, mental difficulties arise which can be more difficult to deal with than the problems of physical health. The most striking of the physical problems is the risk of outbreaks of infectious diseases, of which the common catarrhal respiratory tract infections and their complications are often of most importance. The experience of some investigators suggests that it is in the younger age groups that the sick-rate is greatest, and one cannot ignore the possibility that there may be a reciprocal action between infection and fatigue. Where older children are concerned the difficulties connected with day nursery care are less obvious, so that here one is more inclined to point out the day nurseries' positive contributions to education. The same sort of problems as those indicated above are, however, also met with among older children. In all age groups there are children who, for psychological reasons, find it difficult to fit into the collective life of an institution, and are happy only in the home surroundings, and in all age groups there are children who are very susceptible to infection and are ill off and on as long as they stay in a day nursery.

The medical problems of day nursery care have long attracted the attention of paediatricians. In Sweden, during the nineteen thirties there was a lively discussion, both in the press and in lectures, on day nurseries' advantages and disadvantages. At the time of this discussion the interest of Scandinavian paediatricians was especially directed to the problem of nosocomial infections. The Sixth Northern Pediatric Congress, which was held in Stockholm in 1934 had, as the main subject for discussion, Nosocomial Infections in Children's Hospitals and Institutions, and special attention was given to the significance of respiratory tract infections (Lichtenstein 1935, Gyllenswärd 1935).

In an address given in 1937 and published in the same year, Lichtenstein surveyed the medical side of the care of children in day nurseries and nursery schools. Here he expressed as his definite opinion that collective care of children should be regarded solely as a complement to the ideal state of affairs, which is home upbringing. He described the troubles and risks which accompany the care of children in institutions, and stated the principles which should be followed in the planning, organisation and management

of these institutions. In the report on crèches, children's holiday camps, and other such organisations, which the Population Commission brought out in 1938, there was a detailed analysis of the medical implications of care in day nurseries, nursery schools and similar institutions written by Wallgren. This work treats in detail the task of these institutions from the paediatrician's point of view, the advantages that can be gained, but also the risks to the children's physical and mental health. The standards that should be set by the institutions as regards premises and their arrangement, medical supervision, and the size and training of the staff are described, and the reasons for these statements explained. The section on day nurseries deals specially with the problems of health which are involved, and in particular the risk of epidemics of colds and steps for preventing such occurrences are discussed. The various requirements for rearing children, both physically and mentally, and the care which is recommended for the different age groups are defined. This work forms the basis for the directions on the planning of day nurseries and nursery schools which have been issued by the Social Board jointly with the Medical Board (1944). At the same time standardised instructions to physicians of such institutions have also been brought out by the last mentioned authorities.

The high incidence of illness among day nursery children and the economic consequence of this in relation to hospital beds has been illuminated by Gyllenswärd (1940). He found that while the number of children attending day nurseries in Stockholm during a period of one year in 1937—38 could be reckoned at about 12 per cent of the whole child population of the city, twice this percentage (25 per cent), among children admitted to one of the city's children's hospitals, came from day nurseries. The length of treatment for cases of catarrhal infection of the respiratory tract (the median) was 25 per cent longer for day nursery children than for other children.

The part played by day nurseries in spreading contagious diseases has been studied by G. Melin (1946) in a paper on diphtheria among preschool children in Stockholm. She found that during the years 1942—45 a considerably larger proportion of day nursery children than other children were infected, a fact which showed the day nurseries' role in spreading infection.

The high incidence of upper respiratory tract infections among day nursery children in comparison with children living at home has been further illustrated by Frisell (1948). He started from the assumption that the high frequency of bacterial infections among day nursery children should be reflected in increased sedimentation rates among these children. During the autumn of 1943 he estimated the micro-sedimentation rate on two occasions, separated by a period of 3—4 weeks, in 196 children from three day nurseries in Stockholm. These results he compared with an investigation made at the same time of the sedimentation rates of 266 children who were cared for in their own homes. In the age group 0—2.9 years he found a statistically significant difference between the values for the day nursery and the control children ( $24.0 \pm 1.3$  and  $23.7 \pm 1.4$  in the day nursery group and  $14.9 \pm 0.6$  in the home group, all in mm per hour). A similar difference was established with respect to the day nursery series between the age groups 0—2.9 and 3.0—7 years. Between the values for the latter group and the corresponding control group the difference was inconsiderable.

A comparison between home children and day nursery children has also been made by Bjuggren, Kraepelien and Lind (1948). It concerned 37 children picked at random from a couple of nurseries in Stockholm, and another group of the same number consisting of children cared for in their own home, but with similar circumstances otherwise. Irrespective of possible signs of infections, they were examined three times during the period October 1947 to May 1948 for the occurrence of maxillary sinusitis (X-ray investigation checked by antrum puncture). This condition proved to be very common in both groups, but somewhat more frequent among nursery children. It was, however, obvious that cases with signs of prolonged sinusitis (positive result at all three examinations) were far more frequent in the day nursery group (14 cases) than in the home group (3 cases).

Health conditions among day nursery children has been further dealt with in a Danish publication (Agner 1944). The investigation in question gives a general survey of the situation among children in five representative day nurseries in Copenhagen as it appeared on two different occasions in the same year. The author found that 60.8 per cent of the children needed further observation for medical reasons, and from this he drew the conclusion that regular medical control should be instituted.

American publications dealing with the problem of infection in institutions for children of pre-school age seem to be concerned mainly with nursery schools. The significance of respiratory infections as a cause of a high absence-rate has been pointed out by various investigators (Anderson 1926, Conrad and Jones 1932, Anderson 1934). An investigation into the prevalence of colds in nursery school children (25 children) as compared with a series of non-nursery school children (26 children) has recently been described by Diehl (1949). The observation time was ten weeks. No statistically reliable difference between the two groups was established.

The minimum standard which should be demanded of war-time day nurseries has been defined in a detailed paper by Landon and Thompson (1943). In their section on disease, however, specific infections are dealt with, while respiratory infections are not included.

The most important contributions to the study of health conditions among day nursery children have come from Britain. As a consequence of the increased demands which the conduct of the war placed on women's work, the number of day nurseries in this country increased from 104 in 1939 to 1,550 in 1944, with places for 71,000 children (Mr Aneurin Bevan, 1947). This gave the problem topical interest, and this interest was reflected in a series of reports in the medical press where the authors had often relatively favourable experiences to report concerning the children's health. These authors, however, are concerned mainly with specific infectious diseases among children (Williams 1944, Blonstein 1945, Dow 1945, Forsyth 1947, Nisbet 1947). The importance of catarrhal respiratory tract infections is emphasised, however, by Mackay, Dobbs & Bingham (1945) in a work on the haemoglobin level of children in wartime day nurseries. They found a subnormal haemoglobin level among the children investigated, and connected this with the fact that the incidence of infections, particularly of the respiratory tract, was high; "often nearly every child in the nursery had a running nose and one cold followed close on the heels of another."

From her experiences of two day nurseries in London during a period of three and a half years Menzies (1946) points out that of the children under two years of age a considerable number did not increase satisfactorily in weight in spite of good food, and

that the frequency of infection was high. She further calls attention to the considerable number of children who left the day nursery because of fretting or because they contracted an infection at the nursery. An investigation comparing the occurrence of certain infectious diseases among a group of day nursery children and a group of children cared for at home was published by Allen-Wiliams (1945). The day nursery group consisted of 438 children from 11 day nurseries, while the home group used as a control consisted of 443 children picked out from the registers of the welfare centres in the same localities as the day nurseries so that the groups formed were comparable as regards age and sex. The diseases studied were measles, whooping cough, scarlet fever, pneumonia, otitis media arising as a complication of these diseases, German measles, chickenpox, scabies, impetigo and mumps, but not the common catarrhal infections. Information about the infections that occurred was taken from case records, and gathered from the mothers. The sick-rate was compiled on the basis of the occurrence of all the named infections together during a  $2\frac{1}{4}$  year period, and calculated in terms of the number of cases per 1,000 child months exposed to risk, and it was found to be 41.3 in the day nursery children and 12.1 for the control children, in the age group 0—2 years. In the 2—4 year groups it was 42.7 and 16.8 and in the 4—5 year groups 29.0 and 7.6 respectively. The differences found were greater than those which would be due to chance. The author points out that the infections seem to attack the day nursery groups at an earlier age than the home groups. In the discussion the author mentions the weaknesses in her sources of information, pointing out above all the different standards of supervision of the two groups, and the fact that the records had not been kept for this specific purpose.

An extensive investigation on the occurrence of catarrhal respiratory tract infections was presented the following year by the Day Nurseries Committee of the Medical Women's Federation (1946). This concerned children in the age group 6 months—5 years and compared a group of children registered at a day nursery for at least six months (nursery group I, 2,136 children) with children attending the child welfare centres in the areas of the day nurseries under investigation (2,161 children) as well as with a group that had attended a day nursery for at most one week (nursery group II,

290 children). The comparison was based on the physical condition recorded on one occasion for every child, with respect to enlargement of the tonsillar glands, nasal discharge, mouth-breathing, and physical signs of bronchitis, also weight and general health. The day nurseries investigated were spread over the whole of Great Britain, which meant that the number of investigators was very large. The one investigator, however, within a short period of time, examined both a day nursery and the corresponding welfare centre group. The following results of the comparison between nursery group I and the welfare centre group may be mentioned. The incidence of enlargement of the tonsillar glands was, statistically speaking, significantly higher in the day nursery group, among both boys and girls. This was also the case regarding the nasal discharge and mouth-breathing observed. Bronchitis was also found to be more common among day nursery children but the difference was significant only for the girls. On the other hand, in the observation of the general condition, which was found to apply more to the child's physique than to his state of general health, a higher proportion of "very fit" was found among the nursery children than among the welfare centre children. The former were also, on the whole, heavier than the latter. To ascertain if there was any difference between welfare centre children and day nursery children at the beginning of the latter's day nursery attendance, a comparison was made between the welfare centre group and nursery group II. No difference could be definitely established except with respect to nasal discharge, which was more frequent in the nursery group and was considered to be due to a considerable number of the nursery children having been already infected during the first week in the day nursery.

The research made under the auspices of the above named committee was continued in a later investigation carried out by McLaughlin (1947).

Here also, the investigation consisted of a comparison between day nursery children and a home group. The former were children in eight wartime day nurseries in Birmingham, a total of 557 children while the latter was a group of 641 children who were reared entirely in their homes and lived in the same residential areas as the day nursery children. The day nursery children, whose ages ranged from 0 to 5 years, were divided into seven age groups and the

control material had been chosen to give a corresponding age distribution, but otherwise at random. The investigation period was one year (Nov. 1944—Oct. 1945). During this time the author examined every child as far as was possible once every eighth week, when the physical condition was assessed (in the same way, but more extensively, than in the previously mentioned investigation) and enquiries made concerning infectious illnesses that had occurred since the previous examination. The control groups were examined on the same day as the corresponding day nursery groups. Children who dropped out of the investigation during the year were replaced. On the average, the day nursery groups were examined 3.1 times, home groups 2.4 times. With regard to the statistical results the following may be mentioned. Respiratory tract infections (signs of acute as well as subacute and chronic conditions) were 2—8 times more frequent among day nursery than among home groups, and this difference was manifest in all age groups. The weight of children under two years was found to be lower in the day nursery groups than in the home groups. The opposite was the case with children over this age, which fact was correlated with the extra allowances of rationed foods available to children in day nurseries.

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The investigation into the problems concerning the day-time care of children in Sweden which was commenced by the Population Commission has since been continued, and has, during recent years, been taken over by a special state committee, the 1946 Committee for the care of children partly outside the home. On the initiative of this committee, research has been in progress since 1946 on the medical problems connected with the day-time care of children in the pre-school ages. These activities, of which this work is a part, are being pursued through the co-operative efforts of the Medical Board, the Social Board, the State Bacteriological Laboratory, the State Institute of Public Health and the two Paediatric Clinics of the Caroline Institute.

According to the plan that was drawn up, in the first year the investigations were concentrated on a representative day nursery where the children were under continual observation for the appearance of disease, especially for infections of the respiratory tract.

This is called *Investigation I* in this work. Parallel to this, bacteriological research has been carried out, directed primarily towards establishing the various modes of infection. Guided by the experiences gained in the first year, experimental activity was undertaken in the second year aiming at reducing the morbidity among the children. One of the methods tried was an attempt to prevent completely the entry into the nursery of children with even slight signs of infection. The effects of such a procedure on the incidence of illness have been studied (*Investigation II*). The social and economic consequences have also been a subject of investigation, besides which bacteriological studies similar to those of the previous year have been carried out. In both the above-mentioned investigations I have myself planned and handled the clinical work and the results obtained on these aspects form the subject of the present communication. The results of other aspects of the investigations will be presented by the investigators directly concerned with them, (Professor G. Löfström and Dr G. Melin).

## CHAPTER II

### *Estimation of the morbidity*

#### *The concept "respiratory infections"*

The "respiratory infections" constitute both aetiologically and clinically a very complex group of illnesses. To begin with, the aetiology involves several different micro-organisms. As was shown first by Kruse (1914) and later by Dochez (1930) and his collaborators the infectious common cold is often caused by a specific virus. That epidemic influenza is likewise a virus infection has been further demonstrated by Smith, Andrewes & Laidlaw (1933), also by Francis (1934) and others. The Commission on Acute Respiratory Diseases (1946, 1947 a) has also indicated that other kinds of viruses are aetiologically connected with the appearance of acute respiratory disease.

The syndromes occurring are, however, by no means always confined to the short and often mild symptoms which are characteristic of the primary virus infection. An extremely common occurrence is that bacteria play the part of secondary invaders, causing more prolonged illness and giving the disease its clinical character. This seems to be especially the case with children (Kneeland and Dawes 1932, Kneeland 1935).

It is also known that bacteria can be the primary cause of complaints falling under the heading of respiratory infections, e. g. acute streptococcal tonsillitis. This is also considered to be the case with the common cold (e. g. see Hanger 1948).

Another characteristic observation is that conditions with different aetiologies can occur in forms which, clinically, are not significantly different from each other. Thus a large number of agents can produce the same clinical picture (van Rooyen & Rhodes 1948, Dingle 1948). This must cause difficulties in the individual cases, in a classification based on the aetiology such

as the division of mild respiratory diseases into four different types suggested by the Commission on Acute Respiratory Diseases (1947 b). The differential diagnosis between these forms cannot be made clinically with any great degree of certainty, as was fully demonstrated by the same Commission (1948).

One characteristic of respiratory diseases, on the other hand, is the different forms, symptomatologically speaking, which they can take, and which depend on the region or regions chiefly affected. A classification based on this, such as has been done in rhinitis, pharyngitis, bronchitis etc. in their acute or chronic forms, runs the risk, however, of "merely directing attention to an evident localization and losing sight of the fact that we are really dealing with an underlying disease of more far-reaching potentiality", as pointed out by Brenneman (1945). Besides this there is, to quote Lapin (1948), "the virtual impossibility of segregating grippe, influenza, sore throat, pharyngitis, tonsillitis and cervical adenitis from each other in children".

It is because of the above-mentioned aetiological and clinical characteristics of the respiratory group of diseases that I, in common with e. g. Lapin, decided to give up, in the main, the attempts at classifying them, and to treat them, instead, more or less as one entity. The incidence of this entity in the groups of children forming the subject of this investigation has been considered to be characterized by the occurrence of certain main symptoms which it was possible to record from day to day.

The question of which symptoms are the commonest in respiratory infections in children has been the subject of several investigations.

In a work dealing, among other things, with the clinical symptoms of coryza, bronchitis, sore throat and influenza among members of American medical officers' families, in all nearly 3,000 people, observed for a period of nearly three years, Collins and Gover (1933) made the following observations. Taking all these conditions together, the commonest symptom in all ages was nasal discharge. In young children it was especially frequent. In the 0—4 year group 83 per cent of the cases had nasal discharge, in the 5—9 year group 70 per cent. After that came cough in 59 and 64 per cent, respectively. Fever, like nasal discharge, was very common in young children, occurring in 36 and 39 per cent, respectively. The

occurrence of nasal discharge in the 0—4 year group, with respect to the different complaints, was: in coryza 91 per cent, bronchitis 54 per cent, sore throat 32 per cent, influenza 71 per cent, and fever occurred in 19, 51, 76 and 89 per cent, respectively.

A similar work was presented by van Volkenburgh and Frost (1933). They studied a material of, on the average, 484 Baltimore inhabitants of different ages for a period of two years. They also found that nasal discharge was the commonest symptom of acute minor respiratory diseases and that it occurred in about 90 per cent of the cases in all age groups. Cough was found in 68 per cent. In the 0—4 year group fever occurred in 30 per cent of the cases, in the 5—14 year group in 21 per cent.

Doull, Herman and Gafaer (1933) came to an analogous conclusion in an analysis of cases of minor respiratory diseases encountered in 366 students. They also found nasal discharge to be the commonest symptom, occurring in 90 per cent of the cases, as well as being the commonest at various stages of the illness. Cough was recorded in 56 and fever in 21 per cent of the cases.

The conclusion that apparently can be drawn from the above-mentioned investigations is that in the different forms of the common respiratory infections, nasal discharge, cough and fever are so often present that they can, with a fair degree of certainty, be considered to reflect the occurrence of respiratory tract infections as an entity.

In this work the recording of the morbidity thus includes the occurrence of these three *symptoms*, as well as diarrhoea and vomiting. All these symptoms have in common the fact that they are easy to observe. It was, therefore, considered that the recording of them could be based not only on the observations of the examining staff, but also on information from the children's parents, which information was, of course, checked when possible. Further, these symptoms can be demarcated as to duration. A few of them need some comment.

A "running nose" has been defined as *nasal discharge* in order to obtain the most unambiguous meaning possible. In observing this condition, good guidance was obtained from the presence or absence of crusts or dried secretions around the nostrils. A quite uninfected child can have a clear secretion from the nose, especially after being out in the cold. It proved easy, however, to distinguish

this, and the faint traces left from such a secretion, from true nasal discharge and the thickish crusts and dried secretions it leaves behind.

*Fever* has been defined as a morning or afternoon rectal temperature of  $38^{\circ}\text{C}$  ( $100.4^{\circ}\text{F}$ ) or over. The morning temperature was taken immediately after the child wakened, the afternoon temperature after the child had been lying on his bed for at least half an hour.

Hospitalization was counted as a "symptom" and also fever occurring during such a period.

Certain more or less well-defined *clinical pictures* have also been included, namely otitis, pharyngitis and tonsillitis. The diagnoses in these cases were based on my own observations, or occasionally on those of another physician during hospitalization.

*Otitis*. Although it was noted, when an otitis was recorded, whether the condition was unilateral or bilateral, whether discharge had occurred, and so on, the varying degrees of severity were not used for the present investigation. A bilateral otitis was recorded as *one* otitis, if both ears had been affected at an arbitrarily chosen interval of less than four days.

*Pharyngitis and tonsillitis* have, for practical reasons, been recorded only when accompanied by fever. Owing to the difficulty of differentiating these syndromes they have, in this work, been combined and denoted as "febrile pharyngitis".

The original records included also information on the occurrence of bronchitis, bronchopneumonia and sinusitis. In practice, however, auscultation could only be performed relatively seldom in afebrile cases with a cough. Radiographic examination of the lungs could be performed only in a few of the cases in which bronchopneumonia was suspected on clinical grounds; and special examinations to discover if sinusitis was present could only be undertaken where there was a clear clinical indication. In consequence, such a very considerable under-diagnosing of these syndromes took place that it was not considered suitable to include them, as such, in the present calculations. Their occurrence may nevertheless be said to be reflected, to a large extent, in the symptoms they produced.

The case records include also cases of specific infections encountered, viz. measles, whooping cough, mumps and chickenpox. The symptoms in these infections are, of course, largely the same as those of the common respiratory infections. Knowledge of their

occurrence is therefore necessary. It should be pointed out that the pharyngitis accompanying measles was not specially recorded; nor was any special note made of the vomiting connected with whooping in pertussis.

#### *Morbidity index*

The calculations undertaken in the present work with regard to the sick-rate are based on the following considerations.

The simplest starting point for judging the morbidity due to a certain disease or group of diseases in a material, is to study the total incidence, that is, the number of cases encountered during the observation time. If the material consists of two groups of the same size which are to be compared with each other, and are composed of individuals observed for the same length of time, and during the same period, a direct comparison can be made on the basis of the number of cases observed. If the two groups are of different sizes, the comparison can be based on the number of cases encountered during the observation period calculated in terms of the average number per individual. If, however, the observation times for the two groups also cover different periods, the situation will be more complicated. The sickness-rate would then have to be calculated in terms of the number of cases per individual per unit of time, which is generally denoted as the infection index or morbidity index.

Certain risks, however, accompany such a method of calculation, as, for instance, when it is a question of an infectious disease such as the common cold; in this case, the morbidity in a group under observation must be assumed to bear a certain relation to the morbidity in the population as a whole, during the same period. If, in two groups, the observation period of the one is longer than that of the other, and if the part of the observation period not common to both occurs during a time when the sick-rate is exceptionally high and the risk of infection is correspondingly greater, then the morbidity index of the former group will consequently be displaced in the direction of a higher value than would have been obtained if this group had only been observed for the same time as the other group. This displaced value thus cannot be regarded as representative of the group, in the comparison, although it may express correctly the actual situation.

Fundamentally, the phenomenon is the same if the observation period for two groups covers the same length of time but the groups are composed of individuals with different observation periods; this can cause the number of individuals to vary at different points of time. If, during a period when the morbidity is specially high, the number of individuals in one group is disproportionately large in relation to what it otherwise is during the observation period, the index in this case also will be higher than that which is really representative for the group.

A further difficulty is that it cannot simply be assumed that different attacks of illness can be regarded as independent occurrences. In the case of respiratory tract infections it can be expressed in this way: when an individual has suffered from such an infection, is the risk of his again becoming ill the same as before he contracted this infection? Or is it greater, due to a greater susceptibility having arisen, or less, because a certain immunity has been formed? If a change in the powers of resistance occurs at all, a comparison between various individuals (or groups) with observation periods of different lengths can easily be misleading. If, for instance, a continuous increase in the powers of resistance is assumed to exist, and two groups are to be compared, one of which consists of many individuals with short observation periods, and the other of fewer individuals with longer observation periods but with otherwise similar conditions, the index will point to a greater tendency to sickness in the former group, because the increase in resistance does not apply here to the same extent.

This source of error in the calculation of the morbidity index has been discussed in some detail in a work by Gyllenswärd (1935).

In this work, which deals with the effect of anti-catarrhal vaccination on children in an institution for children of pre-school age, the author used another calculation method. The material in the investigation in question consisted of 247 children, observed for varying lengths of time (half the number at least 3 months) during a period of nearly two years. The author vaccinated every other child, while the remainder formed the control group. In both groups the calculations were based on the attacks of illness accompanied by pyrexia. After standardizing the material with regard to age distribution, and taking into consideration the numbers in the vaccinated group who became ill, and variations in the number of children, the author calculated how many ill children there ought to have been in the control material if the morbidity had been the same there. Then he

compared the difference between the sickness expected and that actually encountered. The author also investigated the length of time occurring between admission to the institution and the occurrence of the first, second etc. illness. He found the interval between the first and second attacks shorter than between the later ones, where it was remarkably constant. He drew the conclusion that the risk of becoming ill is possibly greater during the first period in the institution than later. This in turn means that the advisability of comparisons based on infection indices (number of illnesses per 100 institution days) is questionable.

The changes in resistance which Gyllenswärd considered possible in his above mentioned investigation are the subject of a further analysis in a later work by the same author (1936).

The material was obtained from the same children's home. The investigation covered a period of 5 years, and the total number of children observed was 638. Basing his calculations on the same principles as in the previous work, he found that the incidence of illness was practically the same in the various years, and that the material from different years could therefore be considered as one whole. He calculated the time when the first, second, third illness, and so on, occurred (the median), and found that the interval between the four first illnesses accompanied by a rise in temperature to at least 37.5° C was 5, 6 and 7 weeks, while with a temperature of at least 38° C it was practically constant, 6 weeks. He established, also, that the number of 38° illnesses constantly sinks in proportion to the number of 37.5° illnesses in the successive attacks. The author finally compared the illnesses among children who stayed long enough to have passed the point at which respiratory tract infection was expected, with the number of illnesses actually met with, and found that the relative risk of illness sank as the length of the period in the home increased; the duration of the illness showed the same tendency. The author drew the conclusion that a certain increase in resistance seems to occur, and he repeated his earlier criticism of comparative investigations based on infection indices.

The essential question regarding resistance in acute respiratory tract infections has been dealt with by many other authors in different contexts. Most of them seem to be of the opinion that a relative, transient immunity occurs after infection (e. g. Keefer 1943, Rivers 1943, Topley & Wilson 1946). Support for such an opinion has been found in the work of Dochez (1930), who in experiments on chimpanzees, found an immunity of about 3—4 months, and also by Paul & Freese (1933) who, in their investigation of infection on Spitzbergen, found an immunity of about 7 weeks.

Other authors doubt the existence of any immunity of importance; Brenneman (1945), for instance, emphasizes that even if an attack produces a certain transient immunity, this would be specific, and consequently need not be effective against another infection which could well be of different aetiology. Other authors deny completely the existence of any immunity against common colds; Kanof & Weil (1947), for instance, state without qualification that "previous attacks do not confer immunity", and Thomson & Glazebrook (1941), hold that there is "no evidence of immunity resulting from overt or subclinical attack". The Commission on Acute Respiratory Diseases (1947 c) could not prove from their inoculation experiments that any immunity was produced after an attack of the common cold, and point out the agreement here with certain earlier statistical analyses of the intervals between successive attacks of the common cold (Reed 1934). The results already obtained in British investigations at present in progress point in the same direction (Andrewes 1949).

These research workers have, as is clear from what I have quoted here, dealt with the problem of immunity arising after a single attack of the common cold rather than with the resistance built up over a longer period. Of the investigations dealing directly with the latter problem there can be mentioned, besides Gyllenwärd's work already quoted, the extensive investigation of infection among children in English boarding-schools which was published by the Medical Research Council (1938). Here the attack rate of common colds among boys in six schools before and after an interval of 3 years is compared. One finds "no suggestion of any influence of previous upon subsequent experience in respect of attack rates". Mention should also be made of Löfström's work on acute respiratory tract infections among military personnel (1942). Here he has made a statistical investigation, comparing newly recruited conscripts with conscripts and regulars who had served for at least two months, with respect to their reaction to treatment when suffering from respiratory infections accompanied by pyrexia. No difference between the two groups could be proved. This statement refers, it is true, not to direct morbidity but rather to the degree of severity of the illness, and not to children but to adults; it seems none the less to be of interest in this connection.

The investigations on immunity and resistance against respiratory tract infections clearly do not concur with regard to their results.

The problem is certainly, as Brenneman states, very difficult to get at, and there is reason to agree with Gyllenswärd, who in the latter of his above quoted works (1936) says that only after a number of investigations on this subject have been made will it be possible to obtain a satisfactory view of the situation.

So much, however, could be considered probable, that an increase in resistance following respiratory tract infections is not very strong. This seems to be suggested also by my comparisons of the sick-rate among nursery children with longer and shorter periods of stay in the institution (chap. VII). Accordingly, while the objections to comparative investigations into the morbidity based on the infection index may, in themselves be justified, it seems clear as a practical consequence that such investigations could well be made, provided these objections are taken into consideration when drawing conclusions.

A similar reservation must be made with regard to the previously mentioned risk of making comparisons between groups where the number of individuals varies at different periods. It is, however, clear that the risk of a significant error only arises when an uncommonly high or low morbidity occurs at a time when there are a number of attendance days differing considerably from the average. This risk would seem relatively small, although it must be taken into account.

When, accordingly, my calculations of the morbidity are based on the infection index, it is done with the above stated reservations, which should be considered when judging the results.

Calculations of the infection index, in the usual sense of the word, i. e. the number of cases per 100 child-days, have been used in this work to illustrate the occurrence of certain clinical pictures, viz. otitis, and febrile pharyngitis, also of a couple of specific infectious diseases, namely, measles and whooping cough.

In the light of what has been stated above concerning the characteristics of the respiratory diseases in general, the calculations have otherwise been based on the index for certain symptoms, namely, fever, nasal discharge, cough, diarrhoea, vomiting (here I have also included the hospital stay and fever during such a period). The index refers here to the number of days with a certain symptom per 100 child-days.

This latter method of calculation seems, in some cases, to give a better idea of the situation than the calculations based on the

number that become ill. It thus seems clear that to compare the morbidity in a group where there are long periods of infection, which is a fairly typical feature of day nursery groups, with the sick-rate in a group with shorter periods of infection, as the home material, is not suitable if the comparison is based merely on the number of infections occurring. A better picture in such a case should be given by a comparison of the number of days on which the principal signs of infection are present.

An infection index calculated for one group and covering the whole period of the investigation, or a part of it, implies, in actual fact, a weighed mean of the individual indices of the children in the group, where every child's number of observation days is used as a weight. With this as a basis an analysis of variance has been applied to some of the values obtained (Fisher 1938, Fisher & Yates 1943, Bonnier & Tedin 1940), in order to judge the significance of the differences found.

#### *Signs and criteria of significance:*

P implies the probability that the different groups belong to the same population.

$P \leq 0.05$  implies that there is probable difference between the groups.

$P \leq 0.01$  implies that the difference is very probable.

$P \leq 0.001$  implies that the difference is significant.

d. f. = degrees of freedom.

The analyses of variance made have been concentrated on the indices for fever, nasal discharge and otitis, the first two symptoms being typical and common features of respiratory infections among children, and the latter a typical and relatively common complication.

#### *Gross and net morbidity*

As is described above, the calculations of the morbidity are based, to a large extent, on the determination of the average index for certain symptoms. The morbidity in the different groups, as it mainly reveals itself in the total occurrence of these symptoms, has been denoted as the *gross morbidity*. Such calculations, which include also the occurrence of certain definite illnesses, have been performed in both Investigations.

Certain circumstances, however, reduce considerably the value of this gross record, in so far as the judging of the occurrence of true respiratory infections is concerned. With a view to eliminating these influences the calculations have been corrected in the respects described below, with the result that values for the *net morbidity* have been obtained.

1) During the course of Investigation I there occurred a considerable number of cases of *measles*. These cases are to some extent responsible for the large number of days with fever, nasal discharge and cough. A survey of the cases showed that the symptoms involved in a case of measles generally seem to have occurred during a period of 14 days from and including the first day of fever. During this time, therefore, children with measles were not included. (This also involved the exclusion of a couple of cases of otitis. In these cases, however, the otitis was undoubtedly associated with the attack of measles.)

2) A few *fever* days were due to the occurrence of *mumps* and *chickenpox*. The cases met with had fever for at most two days. The children affected were therefore excluded from the estimates with respect to fever for two days.

3) During the course of the investigations it proved that some children had an almost permanent *serous nasal discharge*, even though, from what could otherwise be judged, they were free from infection. (There were 8 of these children in Investigation I and 7 in Investigation II, as will be mentioned in greater detail in the relevant chapters.) For other reasons also, there seemed justification for assuming that their nasal discharge was of such a strongly allergic nature that, in this respect, they could not be placed on a par with other children. They were therefore excluded from the estimates for nasal discharge.

4) Cases of *whooping cough* were excluded from the estimates for cough from the first day of this illness. Many children cough to a disproportionate extent after the termination of true whooping cough, and the exclusion was therefore extended to include the whole of the remaining observation period. For the same reason children who had had whooping cough the year before the investigation were excluded in respect of cough.

The principle has, accordingly, been to try and obtain a picture of the morbidity among the children if the above mentioned cases

of specific infections and allergic nasal discharge had not occurred. The detailed analysis was based on this calculation of the net morbidity.

#### *Range of the calculation time*

The following considerations were borne in mind when limiting the period on which every child's morbidity was to be calculated. It happened that quite a few children left the institutions during the investigation. Some of them were then well, but many left in connection with an absence due to illness. It would seem only right for this last illness period to be included in the calculations. A "last period of illness", however, would be difficult to limit. One condition for inclusion would also have to be that all children could be observed for a similar length of time after discharge. This has not been possible. Some of the children, it is true, could be followed up for quite a long time afterwards (in general, an attempt was made to follow up every child as long as possible) but others could not be followed up at all after their last day of attendance, in most cases because they moved away. Calculations based on the whole time a child was under observation, therefore, cannot be entirely uniform.

Another possibility would be to terminate the period on which a child's morbidity is calculated at the last attendance day. The result of this, however, would be that the "last illness period", which is so often involved, would have hardly any influence at all, and an under-estimation of the child's total illness would result.

Consideration should also be given to the following situation. In many cases a child was absent for a fairly long time—weeks, and sometimes months—through causes other than illness, usually because the mother was free from work. Sometimes, during such periods, the child attended for a day or so now and then, sometimes not at all. The question now arises as to whether the child should really be counted as an institution child during these periods, for in general the risk of infection would then be considerably less than would otherwise have been the case, and it seems probable that the child's state of health would be influenced in consequence.

One way of endeavouring to preserve the homogeneity of the institution material, arbitrary though it may be, would seem to be

the following. Where a child, during the possible attendance days in a period of one month, is absent owing to "other reasons" for more than the sum of the days when he attended and the days when he was absent through illness, he is excluded from the estimates (exclusion period).

The method which I chose, in consideration of both the problems outlined above, was to carry out parallel calculations along two lines, up to a certain stage. In both cases the calculations for a child began on the first day of attendance, or on the day the investigation began, if he was already attending the institution. Further, of course, a child was wholly excluded when it could not be observed, usually owing to absence from town.

The one estimation is based on the conception "*institution time*". By this is understood, in the following chapters, the time from the first day, as described above, up to and including the last attendance day, less any exclusion periods (and absences due to being out of town). The length of the institution time is denoted, from here on, as the number of *i*-days.

Period III, for nursery school material, Investigation I, constitutes a special case. During 29 of the period's 31 days the institution was closed on account of Christmas holidays. Therefore, during this period, the *i*-days of the groups concerned were calculated on the basis of the remaining time, namely two days.

The other calculation is based on the conception "*observation time*". Here is meant the time from the first to the last day, inclusively, that the child was observed (less any absences due to being out of town). This time is denoted from now on as *o*-days.

The purpose of the two methods of calculation just defined has been to try to give both a general picture of the morbidity among institution children during the whole time they were observed, and also a picture of the morbidity during the periods when they could be counted as institution children in the narrow and real sense of the word. Of these two methods, the latter seems more likely to answer the questions proposed, and the final analyses as well as certain special calculations, have therefore been based on this.

In the control material in Investigation I, consisting of children cared for entirely in their homes, only one time concept, the observation time, was for natural reasons used.

The questions just mentioned have also been discussed by other investigators. In the work mentioned earlier by Mackay, Dobbs & Bingham the "last illness period" and the problems of its treatment is mentioned. These authors chose to terminate the calculations for a child on the last attendance day. In a work on the effect of ultra-violet irradiation on the frequency of colds among students the authors (Doull, Hardy, Clark & Herman 1931) excluded from the investigation a person who was absent from treatment more than three days in a week.

## CHAPTER III

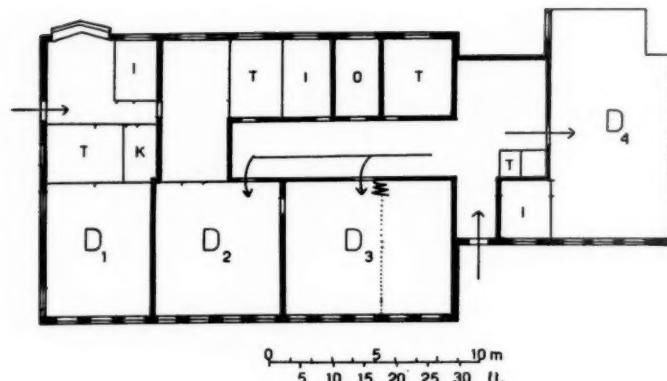
### *Investigation I*

The aim of this investigation has been to illustrate the occurrence of respiratory infections among children in a representative Swedish day nursery which was run according to current principles and where no special steps to prevent infection had been taken. To provide further information the investigation includes parallel observations of children attending a nursery school attached to the day nursery in question, and also of children cared for entirely in their own homes.

#### *Institution investigated*

The institution investigated is situated on an island within the boundaries of Stockholm, and it is the only one of this type there. Almost all the children who are included in this investigation are resident on this island. It has an area of about 0.75 sq. kilometers (= 185 acres) and contains mainly 3—4 storey blocks of flats built during the last few decades and containing flats ranging from one room, hall and kitchen, to two or three rooms and kitchen. There are also a fair number of houses generally inhabited by one family, on the island. Nearly all the homes are equipped with central heating and bathrooms. The general standard of the buildings can accordingly be regarded as relatively high.

The population of the island, about 7,000 persons, also has a relatively high economic and social standard. The breadwinners are for the most part office workers or skilled workers of good standing, but some run their own concerns or are professional people. A more detailed description of their circumstances is given later in the paragraph on the home group.



*Fig. 1. Plan of the Day Nursery studied in Investigation I. D<sub>1</sub>, 2, 3, 4 = the different departments. T = toilet rooms. I = isolation rooms. O = superintendent's office.*

#### Premises

The institution premises are situated in a special two-storey building and on the ground floor of a block of flats built in one with it. The plan of the day nursery is shown in fig. 1. Details with regard to the different departments are given in table 1; these designations are the same as those that will be used for the different

**Table 1. Character and Details of the Various Departments Investigation I**

Character	Age	No. of places	Floor area	
			m <sup>2</sup>	sq. feet
D <sub>1</sub>	Day Nursery	6—15 mths.	9	32.0 344.5
D <sub>2</sub>	do.	15 mths.—3 yrs.	12	59.8 643.8
D <sub>3</sub>	do.	3—4½ yrs.	15	51.0 549.0
D <sub>4</sub>	do.	4½—7 yrs.	15	61.0 656.7
N <sub>1</sub>	Nursery School	3—5 yrs.	15—20	39.1 420.9
N <sub>2</sub>	do.	4—7 yrs.	15—20	75.0 807.4
N <sub>3</sub>	do.	4—7 yrs.	15—20	39.1 420.9
N <sub>4</sub>	do.	4—7 yrs.	15—20	75.0 807.4

groups. The age limits, number of places, and the play and sleeping space available for the various groups are also shown in the table.

The day nursery departments D<sub>1</sub>, D<sub>2</sub> and D<sub>3</sub> are situated on the ground floor of the smaller building. The nursery school is situated in the basement, as is also the kitchen, and other similar departments. The upper storey contains some of the staff's quarters. The day nursery department D<sub>4</sub> and the entrance hall are situated a half storey below the ground floor of the smaller building; this is not clearly shown on the plan.

From the table it can be seen that the rooms allotted to the day nursery children are relatively adequate in size. They exceed the minimum demands which are laid down by the Social Board (3 square metres = 32.3 sq. ft. per child). Similar to the practice in other day nurseries, it not infrequently occurs, however, that considerably more children are placed on the lists than the number of places allows, consideration being taken to the fact that absences can be expected. The number of children present in a group can therefore occasionally considerably exceed the number allowed.

The infants' department D<sub>1</sub>, as will be seen, has its own entrance and is relatively well separated from the other departments. There is, however, one means of communication with department D<sub>2</sub>. This door is normally kept closed, but it must be used by the staff several times a day. Departments D<sub>2</sub>, D<sub>3</sub> and D<sub>4</sub> have a common entrance and hall. Between departments D<sub>2</sub> and D<sub>3</sub> there is a direct communication in the form of a door, while department D<sub>4</sub> lies relatively separate. Department D<sub>2</sub> has its own toilet rooms, departments D<sub>3</sub> and D<sub>4</sub> have theirs in common. There are three isolation rooms available, for departments D<sub>1</sub>, D<sub>2</sub> and D<sub>3</sub> + D<sub>4</sub>.

The nursery school has its own entrance and is also in other ways well separated from the day nursery. The hall is common to both departments.

There is also included in the construction of the building a balcony outside department D<sub>1</sub>, intended for infants' beds, and an enclosed playground. The building has central heating and was constructed in 1945. Although the institution is modern and can be considered relatively well adapted to its purpose, it has certain deficiencies, such as the inadequate possibilities for the isolation of the various departments indicated above.

### *Staff*

The institution is run by a female superintendent with extensive experience of day nurseries and nursery schools. In the day nursery, the oldest group, D<sub>4</sub>, is run by a nursery school teacher, assisted by a pupil. The three other groups are in the care of two nursery nurses to each group. Another nursery nurse is employed as relief between groups D<sub>1</sub> and D<sub>2</sub>. The nursery school groups are taken by two nursery school teachers, each assisted by one or two pupils.<sup>1</sup> In the kitchen and laundry three people are employed. The total staff accordingly consists of 17—19 people, apart from part-time cleaners.

### *Daily routine of the institution*

The *day nursery* is open every week-day between 6.30 a. m. and 6.0 p. m. (On Saturdays it is closed at 2 p. m.) The children arrive in the morning at different times, the first punctually at 6.30 a. m., the others one after the other during the next couple of hours or so. Between 6.30 a. m. and 8.0 a. m. however, only one member of the staff is on duty. This means that the children who arrive during this period, up to 20 children, are gathered in one room until the staff is complete. Infants are an exception, being put in their own room from the beginning. From the point of view of the spread of infection, the fact that the children from the three other groups mix with each other in this way is obviously significant. From 8.0 a. m., however, all children stay in their own departments, and there is no further indoor intimate contact between the groups except as a chance occurrence. Considerable possibilities for contact exist, however, as has been shown above.

The daily routine for the various groups is roughly as follows: Infants are bathed after arrival and clad in day nursery clothes. Then they sleep until 10.0 a. m. when they are given their second feed. (The first has been given at home.) After that they are put outside till the 2.0 p. m. feed. The older children have breakfast at 8.0 a. m. and play indoors afterwards until 9.30 a. m. Then they are out-of-doors until 12 o'clock, when they have their midday dinner. Then they rest till 2.30—3.0 p. m. and at 3.30 p. m. they

<sup>1</sup> The Swedish nursery school teachers have a two year training in special training schools. The nursery nurses have a 6 months' course.

have a light meal. After this the children play indoors, sometimes out-of-doors, till they are fetched home by their parents. They have then spent an average of about nine hours in the nursery. This routine was followed during the winter half of the year, the period mainly covered by the investigation. During the summer the children of course play outside for a longer time.

The diet the children receive is, with minor variations, illustrated by the following menus.

*Infants:* 10.0 a. m. Gruel made with flour, or porridge and milk plus fruit juice or rose-hip tea.

2.0 p. m. Various kinds of mashed vegetables, possibly with meat or fish, and thickened fruit juice.

*Older children:* 8.0 a. m. Gruel made with flour, and bread and butter, often with cheese or whey-cheese.

12 o'clock. Midday dinner, for instance according to the week's menu given below.

Monday: fried sausage with macaroni, thickened fruit juice.

Tuesday: vegetable soup, corn flour pudding.

Wednesday: minced meat and potatoes, fruit juice jelly and milk.

Thursday: pea soup and pancakes.

Friday: boiled or fried fish, thickened rose-hip juice.

Saturday: oatmeal pudding.

3.30 p. m. Rose-hip tea, fresh fruit or fruit juice and bread and butter, possibly also warm milk or cocoa.

All children receive 10 drops of Guttae adevitamini daily (= about 2,500 I. U. vitamin A and 1,000 I. U. vitamin D).

*The nursery school* is open every week-day except Saturdays. The children stay three hours. If the weather is suitable they spend part of this time outside. They receive no food at the school. Fairly free contact exists between the two groups which simultaneously attend the nursery school but the nursery school children have no contact worth mentioning with the day nursery children.

A point that is essential to the investigation is the degree to which infected children were admitted to the institution. It should be pointed out that the decision in such questions was made by the superintendent or those in charge of the groups. In accordance with the investigation's purely observational task, the investigators always endeavoured not to influence these decisions. The principles on which the decisions were based were essentially liberal, and this feature should be reflected in the results of the

investigation. It does not seem probable, however, that they deviated to any significant extent from what is the usual practice in most of the similar institutions.

#### *Home group material*

From among the factors which might conceivably affect the child's circumstances with respect to sickness, especially with regard to respiratory infections, and which it was possible to record and consequently to use as a basis in the selection of the control material, the following were selected.

- 1) Child's age.
- 2) Child's sex.
- 3) Size of the family.

Here the number of adults, including any lodgers, were counted, and the number of children under 16 years. In case brothers and sisters of school age should constitute a bigger risk factor, from the point of view of infection, than other siblings, these were recorded separately.

- 4) Home.

Here the number of ordinary rooms were recorded, attention also being paid to the presence or absence of a hall, dining recess, and kitchen.

- 5) Family's socio-economic status.

A rough division into three groups was made. Most of the bread-winners on the island were, as mentioned earlier, office workers or skilled workers. Their families have been placed in group 2. There was also a smaller number of civil servants, civil engineers, dentists, and so on, who were placed in group 1, and a small number of families in poor circumstances (casual labourers, unmarried mothers, and so on), classified as group 3. This classification, which was established for each child in co-operation with the health visitor stationed on the island is necessarily rather rough. Group 2 especially is rather wide. It refers, however, merely to a general situation.

All the children who were expected to belong to the institution during October 1946 were graded on the basis of these five aspects. With a few exceptions the children registered with the island's Child Welfare Centre were dealt with in the same way. These exceptions were, besides the institution children themselves, children with brothers or sisters at the day nursery or nursery

school or children who had themselves earlier attended such an institution. Further, infants under six months were not included, nor were children who were expected to move from the island shortly, and finally a few children belonging to families from whom, in the health visitor's opinion, no co-operation could be expected.

From the remaining material, about 450 children between 6 months and 7 years of age, a preliminary series of 138 home children was then chosen, care being taken as far as possible to ensure that the characteristics of the groups would coincide with those of the corresponding institution groups. A circular was sent round to the parents where aims of the investigation were explained and their co-operation requested. Shortly afterwards, they were visited by one of my assistants, an experienced health visitor who explained in more detail the course of the investigation planned. It was specially emphasised that we desired information regarding even the slightest signs of illness, such as a mild nasal discharge or cough. Agreement to co-operate was obtained in the case of 119 children, while 16 could not be included as they had already begun school or were about to move away or for other reasons, and three refused to take part. Besides these, however, 18 children entered the investigation. They were included because their parents insisted, saying that otherwise they would not allow their other children—those who were really wanted for the investigation—to take part. The number in the home group was therefore 137. During the course of the investigation, however, it became clear that the reports from the homes of three children were at times not very careful, and that the results for these could not be considered fully reliable. They were therefore excluded in the final analysis. The remaining home material, accordingly, consisted of 134 children. Co-operation was established with the parents of these children and continued throughout the investigation in all cases except nine. Of these, three were added ~~six months~~ <sup>two weeks</sup> after the investigation had begun, while four left the town at different periods during the spring, and the other two were admitted to the nursery school and day nursery in February and March, respectively.

Co-operation with the parents proved extremely easy to establish. They obviously appreciated the advantage of being offered easily accessible, free advice on their children's health, and medical

attendance when they were ill, and they proved, with the three above-mentioned exceptions, very positive in their attitude both to sending in reports and also to bringing the child in for examination on request.

#### *Method of the investigation*

##### *Day nursery and nursery school children*

A circular like that sent to the parents of the home group was sent to the parents of the day nursery and nursery school children requesting their co-operation. In particular they were asked to ring up if the child, for one reason or another, was away from the institution, so that contact could be established immediately. A personal interview with the parents was arranged as soon as possible so that, among other things, the child's family and personal history could be recorded. As soon as possible the child was subjected to a thorough examination. All the children were also examined in October or November by an ear, nose and throat specialist, with whom an arrangement had been made to co-operate throughout the investigation. Attention was particularly directed to the occurrence of suspected allergic rhinitis or adenoids. A great many of the children were found to have such large adenoids that, according to current practice, they should have been removed. The parents, in these cases, were advised to give their consent and an opportunity was given for the operation to be performed, free of cost, shortly afterwards. This was done in the case of 20 children. Another similar examination of the institution children, including both a general and a special ear, nose and throat examination, was made in April and May 1947.

During the whole period of the investigation all the children were inspected and records made by my assistant every day that the institution was open. Here the occurrence of nasal discharge and cough and other signs of infection were noted.

On an average of twice a week I myself examined every group. I then recorded, besides the above-mentioned signs of infection, the occurrence of definite pharyngitis or tonsillitis, and any further examinations required were performed (otoscopy, auscultation, etc.).

Absences from the institution were recorded daily and a note made of whether they were due to illness or other causes. This had

generally been spontaneously reported by the parents in accordance with the request that had been made. If the absence covered one or two days and the reason had not been reported, contact was established with the home by telephone or a visit. Almost invariably in such cases the child was home because the mother was free from work or some such reason. In practically no instance was the cause that the child was ill. In these latter cases the reporting system worked nearly perfectly after a very short time. On the whole, co-operation with the parents of the institution children also proved very easy to obtain; their attitude to the investigation was positive throughout and they gave their assistance willingly.

Reports were usually made by telephone, and when a child was reported ill at home the person giving the message, usually the mother, was questioned in such a way as to yield information that could be recorded in a similar manner to the observations made in the institution. The occurrence of nasal discharge was discussed on the basis of the definition given further back. Other information (if there was cough, vomiting etc.) could generally be accepted direct.

A large number of the reports as to illness, however, made it advisable for me to visit the home. A desire to attain the highest possible certainty and uniformity in the observations made the indications for these visits rather extensive. I have accordingly visited sick children at home

- 1) when it was required for making a diagnosis;
- 2) in all cases of fever;
- 3) whenever it seemed necessary for other medical reasons;
- 4) at the request of the parents.

The treatment prescribed can be said to have corresponded to usual paediatric practice. In simple respiratory infections with fever of short duration I insisted that the patient should be confined to bed for at least 24 hours after the temperature had returned to normal. In uncomplicated cases sulphonamides were not generally given. If, on the 3rd or 4th day, the temperature remained high, sulphonamides were introduced in full dosage. At the least sign of otitis sulphonamides were instituted at once; more severe cases were referred immediately to the ear, nose and throat specialist for special treatment. When hospital treatment was required the child was admitted to Norrtull's Hospital, generally to the ward where I myself was working, or to the Eastman Institute's E.N.T. department for children.

### *Home group*

All the children in the home group were examined once during October—November 1946 and once during April—May 1947. The same sort of examination was made as was described previously in connection with the institution children. In this group also, some parents were urged to consent to their children's adenoids being removed. Adenoideectomy was performed in 31 cases. (A larger proportion of the home group than of the institution group were considered to need operation, this being probably due, at least in part, to the fact that relatively more of the latter children had already been operated upon.)

The recording of the home group's morbidity was based on information from two sources, the parent's own reports and the investigating staff's examinations.

The parents had, as was mentioned earlier, been asked from the beginning to report as soon as they noticed any signs of illness in their children, however slight, and then to supply frequent reports as to the child's condition. This appeal was repeated both verbally and in writing several times during the course of the investigation, and its importance stressed. Attention has already been called to the helpful attitude of the parents throughout the investigation. To facilitate contact with them, a telephone period of 1½ hours every week-day morning on a special line was arranged, and it can perhaps serve as an illustration of the intimate contact established with the children's homes to mention that a telephone queue had very often to be arranged during this period.

Concerning reports from the parents, and the evaluation of these, the reader is referred to what has been previously written with regard to the institution children.

The observations on the home group recorded by myself or my assistant were made on various occasions. The two examinations of the whole material carried out during the autumn and spring have been described earlier. All the children in the home group were, besides this, sent for to be examined once every other month. About half the home group was sent for once a month and a small proportion even more often for special examinations (haemoglobin content, sedimentation rate). The home children corresponding to the day nursery children were visited in their homes by nurses once a month

for the taking of bacteriological tests, irrespective of whether any report of illness had been sent in or not. On all these occasions, of course, a check was made of the child's condition. Only very occasionally were symptoms of illness noted which the mother should have observed and reported, but of which nothing had been heard.

As was the case with the institution children, a large number of the reports made it necessary for me to visit the home. The indications for this were the same for the home group as for the institution children.

At regular intervals the material was looked over to see if any child had not been heard of for two weeks. Contact was immediately established with the parents in such cases, to find out if anything had happened that should be recorded. Such contact was made, if possible, by a home visit, in order that the child could be inspected.

It must be pointed out that these frequent reports and the intensive observation of the home material were made possible, or at any rate facilitated, by two factors. One was that all the homes of the home group lay within an easy ten minutes' walk of the institution. The other was that almost all these parents either had a telephone or else had easy access to a telephone in a neighbour's flat. Both these factors applied to practically the same extent in the case of the institution children.

The total number of examinations of the children in the home group amounted to 1,584, of which I performed 571 and my assistants 1,013, which makes an average of about 1.5 examinations per child per month. Further details regarding the examination of the children will be found in the accompanying tabulation.

*Home visits to institution and home group children*

	Self	Assistants
Day nursery children (D).....	130	73
Home group children corresponding to (D)...	167	443
Nursery school children (N).....	175	16
Home group children corresponding to (N)...	112	156

*Examination of home group children at the consultation room*

	Self	Assistants
Home group children corresponding to (D)...	175	307
Home group children corresponding to (N)...	117	107

In spite of all the attempts made to ensure that the supervision of the home group would be thoroughly adequate, there is still, of course, a certain risk that infections of short duration, in particular, may have been overlooked to a slightly greater extent in the home group than in the institution group. With a view to reducing the consequences of this in the results of Investigation I, nasal discharge or cough unaccompanied by fever occurring for periods of less than three days have not been included.

### *Calculations and results*

#### *Classification of home group material*

As mentioned earlier a preliminary home group had been chosen, based on certain characteristic features (age and sex distribution, home circumstances) in the groups of children expected to attend the institution in October 1946. On the 15th October, however, when the investigation was already in progress, it was found that the composition of these groups to some extent diverged from what had been anticipated. Some children who had been enrolled had not come, and others had been admitted in their place. In some respects, also, the home group differed from what had been contemplated in the beginning. A new classification of the latter group was therefore made on the basis of the conditions prevailing with respect to the institution groups at the time. Accordingly, home groups corresponding to the day nursery groups, and denoted as  $H_{D_1}$ ,  $H_{D_2}$ ,  $H_{D_3}$  and  $H_{D_4}$ , respectively, were worked out. In the same way, I arranged a home group,  $H_{N_1}$ , corresponding to the nursery school group  $N_1$ , while a common home group,  $H_{N_2-4}$ , corresponded to the three older nursery school groups.<sup>1</sup>

The characteristics and number of children in the various institution and home groups on Oct. 15, 1946 are shown in table 2. In the calculation of the averages for the whole day nursery and nursery school respectively, as well as for the corresponding home material, weighing was done, with the number of children in

<sup>1</sup> The material was further classified so that in each home group average characteristics for boys and girls separately would be comparable with those in the corresponding institution material. As further calculations showed (chap. V), however, the differences in the sick-rate of the sexes did not seem to necessitate a continuation of this system of classification.

the institution groups used as weights. The last column gives the average taxable incomes of the various families estimated for the state income and property tax in 1946. This measure was undertaken to discover whether the subjective classification into the three socio-economic groups had an objective basis. Information was available for 260 of the 272 children. It is clear that a relatively good negative correlation exists.

It can now be seen from the table that the agreement between the institution and home groups, as far as age is concerned, can be regarded as consistently good; the same is the case as regards the size and composition of the family and the home conditions. As regards the income and social level the agreement is good for the nursery school groups, but not so good for the day nursery children, especially groups  $D_2-H_{D_2}$ .

This is partly due to the following situation. As mentioned earlier, the final home group obtained differed from the one that had been planned, seeing that 19 of the children whose inclusion was intended at the beginning, could not be included while 18 others were accepted in their place. These 18 children belonged in the main to a higher income and social group than the other 19, because they were mainly younger brothers and sisters of the children in the home group corresponding to the nursery school children. Because of their low age they had, in many cases, to be placed in the groups to be compared with the day nursery children, if they were to be included in the calculations at all. A preliminary calculation of the morbidity in the different home groups now showed that no significant difference existed between children in different socio-economic groups whose other characteristics were alike. (This point will be enlarged upon later, chapter VI.) I have therefore considered that there is no objection to including the children in question.

It can, however, be noted that the day nursery children's parents, in spite of the fact that some of them were considered to belong to lower socio-economic groups, had in fact, approximately the same incomes as the home group parents. This is connected of course with the fact that in the case of the first-mentioned families both parents were often working, thus bringing in a relatively high income, while the standard of the home appeared to the health visitor not to be so good as the income suggested.

**Table 2. Age and Social Conditions**  
**Comparison between Institution and Home Groups**  
**Investigation I**

Date survey made	Group	No. of children	Mean age in months	Mean no. of members in family			Mean no. of rooms in home			Socio-economic group	Mean annual income (Sw. Crowns)		
				Adults	Children		Bed & living rooms	Hall or dining-recess	Kitchen				
					All ages	School age							
Oct. 15 1946	D <sub>1</sub>	7	12.0	2.0	1.3	0.3	1.4	0.6	1.0	2.3	7,978		
	D <sub>2</sub>	16	24.7	2.1	1.2	0.1	1.2	0.1	1.0	2.5	9,115		
	D <sub>3</sub>	22	41.0	2.0	1.3	0.1	1.1	0.2	1.0	2.3	5,877		
	D <sub>4</sub>	23	60.2	2.0	1.7	0.1	1.5	0.1	1.0	2.4	5,269		
	D <sub>1-4</sub>	68	40.7	2.0	1.4	0.1	1.3	0.2	1.0	2.4	5,944		
	H <sub>D1</sub>	15	11.5	2.1	1.4	0.1	1.6	0.5	1.0	2.1	7,523		
	H <sub>D2</sub>	31	24.8	2.0	1.5	0.0	1.4	0.5	1.0	2.0	7,348		
	H <sub>D3</sub>	20	44.1	2.0	1.4	0.1	1.2	0.4	1.0	2.2	5,811		
	H <sub>D4</sub>	17	63.6	2.1	1.8	0.2	1.1	0.5	1.0	2.2	5,056		
	H <sub>D1-4</sub>	83	42.8	2.0	1.6	0.1	1.3	0.5	1.0	2.1	6,140		
	N <sub>1</sub>	16	42.5	2.0	1.8	0.1	1.8	0.2	1.0	1.9	7,809		
	N <sub>2</sub>	21	57.6	2.1	2.0	0.2	2.5	0.4	1.0	1.6	12,597		
	N <sub>3</sub>	19	54.5	2.1	2.4	0.5	2.7	0.4	1.0	1.8	11,100		
	N <sub>4</sub>	17	68.1	2.1	1.9	0.1	2.4	0.8	1.0	1.6	11,728		
	N <sub>1-4</sub>	73	55.9	2.1	2.0	0.2	2.4	0.4	1.0	1.7	10,958		
	H <sub>N1</sub>	16	42.4	2.1	1.6	0.3	1.7	0.4	1.0	1.8	7,667		
	H <sub>N2-4</sub>	32	61.8	2.0	2.0	0.3	2.0	0.7	1.0	1.8	10,100		
	H <sub>N1-4</sub>	48	56.7	2.1	2.0	0.3	2.0	0.6	1.0	1.8	9,856		
Feb. 1 1947	D <sub>1</sub>	6	11.3	1.8	1.3	0.5	1.2	0.5	1.0	2.2			
	D <sub>2</sub>	13	27.4	2.0	1.2	0.2	1.4	0.3	1.0	2.4			
	D <sub>3</sub>	14	45.8	2.1	1.1	0.1	1.2	0.2	1.0	2.4			
	D <sub>4</sub>	18	64.3	2.1	1.7	0.2	1.5	0.2	0.9	2.4			
	D <sub>1-4</sub>	51	43.6	2.0	1.4	0.2	1.4	0.3	1.0	2.4			
	H <sub>D1</sub>	15	15.5	2.1	1.4	0.1	1.6	0.5	1.0	2.1			
	H <sub>D2</sub>	32	29.1	2.0	1.5	0.0	1.3	0.5	1.0	2.0			
	H <sub>D3</sub>	20	48.1	2.0	1.4	0.1	1.2	0.4	1.0	2.2			
	H <sub>D4</sub>	17	67.6	2.1	1.8	0.2	1.1	0.5	1.0	2.2			
	H <sub>D1-4</sub>	84	46.3	2.0	1.6	0.1	1.2	0.5	1.0	2.1			

(Continuation from previous page.)

Date survey made	Group	No. of child- ren	Mean age in months	Mean no. of members in family		Mean no. of rooms in home			Socio- econo- mic group	Mean annual income (Sw. Crowns)	
				Adults	Children		Bed & living- rooms	Hall or dining- recess	Kit- chen		
					All ages	School age					
Feb. 1 1947	N <sub>1</sub>	12	48.2	2.0	2.2	0.1	2.3	0.3	1.0	2.0	
	N <sub>2</sub>	21	61.7	2.1	2.0	0.2	2.4	0.5	1.0	1.7	
	N <sub>3</sub>	17	55.2	2.1	2.5	0.5	2.8	0.2	1.0	1.8	
	N <sub>4</sub>	18	72.0	2.1	2.1	0.2	2.1	0.6	1.0	1.7	
May 1 1947	N <sub>1-4</sub>	68	60.4	2.1	2.2	0.3	2.4	0.4	1.0	1.8	
	H <sub>N1</sub>	16	46.4	2.1	1.6	0.3	1.7	0.4	1.0	1.8	
	H <sub>N2-4</sub>	34	64.6	2.0	2.0	0.4	1.9	0.7	1.0	1.8	
	H <sub>N1-4</sub>	50	61.4	2.0	1.9	0.4	1.9	0.6	1.0	1.8	
May 1 1947	D <sub>1</sub>	7	13.1	2.1	1.3	0.3	1.1	0.4	1.0	2.1	
	D <sub>2</sub>	16	25.1	2.1	1.2	0.1	1.4	0.3	1.0	2.3	
	D <sub>3</sub>	19	48.6	2.1	1.1	0.1	1.3	0.2	1.0	2.4	
	D <sub>4</sub>	18	64.1	2.0	1.6	0.2	1.4	0.2	0.9	2.5	
	D <sub>1-4</sub>	60	42.8	2.1	1.3	0.2	1.3	0.3	1.0	2.4	
	H <sub>D1</sub>	15	18.5	2.1	1.4	0.1	1.6	0.5	1.0	2.1	
	H <sub>D2</sub>	29	32.3	2.0	1.5	0.0	1.3	0.5	1.0	1.9	
	H <sub>D3</sub>	20	51.1	2.0	1.4	0.1	1.2	0.4	1.0	2.2	
	H <sub>D4</sub>	17	70.6	2.1	1.8	0.2	1.1	0.5	1.0	2.2	
May 1 1947	H <sub>D1-4</sub>	81	48.1	2.0	1.5	0.1	1.2	0.5	1.0	2.1	
	N <sub>1</sub>	13	52.4	2.1	2.1	0.2	2.2	0.2	1.0	1.8	
	N <sub>2</sub>	21	65.5	2.1	2.0	0.3	2.5	0.5	1.0	1.7	
	N <sub>3</sub>	15	55.1	2.1	2.3	0.5	2.9	0.3	0.9	1.6	
	N <sub>4</sub>	14	74.0	2.1	2.1	0.1	2.0	0.7	1.0	1.7	
	N <sub>1-4</sub>	63	62.2	2.1	2.1	0.3	2.4	0.4	1.0	1.7	
	H <sub>N1</sub>	16	49.4	2.1	1.6	0.3	1.7	0.4	1.0	1.8	
	H <sub>N2-4</sub>	31	67.5	2.0	2.0	0.4	1.9	0.7	1.0	1.8	
	H <sub>N1-4</sub>	47	63.8	2.0	1.9	0.4	1.9	0.6	1.0	1.8	

At the beginning of the investigation the children at the institution filled all the available places. It was considered therefore, that the composition of the various institution groups would remain fairly constant. Quite a number of children, however, left the institution at different times, and others were taken instead. Further, certain moves within the institution could not be avoided. Minor changes occurred also, as mentioned earlier, within the home groups. Table 2 also illustrates the situation in the different groups on Feb. 1 and May 1, 1947.

The table shows that the comparability between institution and home material was largely unchanged in the two latter surveys, apart from the question of age. The average age for the day nursery groups changed only to a minor extent, so that the difference between the average ages of groups  $D_{1-4}$  and  $H_{D_{1-4}}$  increased successively. As will be shown later in more detail (chap. VI), the differences in the morbidity between the various age groups within the home material ~~were~~, however, not so great that an age difference of the magnitude in question here would be likely to make the groups unduly unrepresentative.

#### *Investigation time*

The observations were begun on Oct. 1, 1946. They did not cover the whole material until after a few days, however. The date Oct. 15 has therefore been taken as the starting point for the calculations. The investigation period has been divided up as follows: —

Period	I	15. 10. 1946—14. 11. 1946
	II	15. 11. 1946—14. 12. 1946
	III	15. 12. 1946—14. 1. 1947
	IV	15. 1. 1947—14. 2. 1947
	V	15. 2. 1947—14. 3. 1947
	VI	15. 3. 1947—14. 4. 1947
	VII	15. 4. 1947—14. 5. 1947
	VIII	15. 5. 1947—31. 5. 1947

All these periods apply for the day nursery as well as for the corresponding home group material. The nursery school finished its activities for the term on May 14, 1947, and the calculations for this as well as for the corresponding home group material therefore include only periods I—VII.

The nursery was closed for the Christmas holidays Dec. 24, 1946—Jan. 1, 1947 and owing to a measles epidemic between Feb. 6 and Feb. 19, 1947. The nursery school was closed for the Christmas holidays Dec. 14, 1946—Jan. 12, 1947 and through the measles epidemic Feb. 1—Feb. 23, 1947.

#### *Scope of the material*

Investigation I included 103 day nursery children, 96 nursery school children and 134 home group children. Their distribution on the different groups is shown in tables 3 and 4.

**Table 3. Total Number of Children in the Institution Groups  
Investigation I**

	D <sub>1</sub>	D <sub>2</sub>	D <sub>3</sub>	D <sub>4</sub>	N <sub>1</sub>	N <sub>2</sub>	N <sub>3</sub>	N <sub>4</sub>
Boys .....	11	16	17	14	11	12	9	14
Girls.....	9	11	17	15	14	13	19	14
Boys + Girls...	20	27	34	29	25	25	28	28

**Table 4. Total Number of Children in the Home Groups  
Investigation I**

	H <sub>D<sub>1</sub></sub>	H <sub>D<sub>2</sub></sub>	H <sub>D<sub>3</sub></sub>	H <sub>D<sub>4</sub></sub>	H <sub>N<sub>1</sub></sub>	H <sub>N<sub>2-4</sub></sub>
Boys.....	7	18	10	9	7	20
Girls.....	8	14	10	8	9	14
Boys+Girls	15	32	20	17	16	34

On account of changes within the institution, one or two of the children are included as a member of two groups.

As one child in each of groups D<sub>3</sub> and D<sub>4</sub> (owing to many absences) has only been included in the calculation of the observation time, the total number of day nursery children who are included in the calculations of the institution time is 101.

#### *Gross morbidity*

The results of the calculations of the gross morbidity in the various groups of institution and home children are shown in

**Table 5. Gross Infection Indices**  
**Investigation I**

Group	F e v e r				H o s p i t a l i z e d				N a s a l		C o u g h	
	38° C		39° C		Total		With fever		discharge			
	i	o	i	o	i	o	i	o	i	o	i	o
D <sub>1</sub>	3.80	4.04	1.51	1.60	2.11	3.54	0.42	0.45	43.18	42.08	26.18	26.79
D <sub>2</sub>	4.25	4.01	2.09	1.94	1.11	1.25	0.29	0.32	66.03	58.83	40.54	35.76
D <sub>3</sub>	2.39	2.45	0.83	0.71	1.35	1.41	0.08	0.12	47.17	44.22	22.44	26.64
D <sub>4</sub>	2.40	2.52	1.21	1.18	0.45	1.16	0.05	0.09	49.77	47.72	31.67	32.56
H <sub>D1</sub>	2.95		1.05		0.38		0.15		24.11		14.37	
H <sub>D2</sub>	1.96		0.81		0.07		0.01		21.60		13.47	
H <sub>D3</sub>	1.55		0.52		0.85		0.11		20.40		18.69	
H <sub>D4</sub>	1.21		0.29		0		0		21.07		12.80	
N <sub>1</sub>	3.39	3.57	1.14	1.16	0	0	0	0	44.09	43.20	26.89	27.64
N <sub>2</sub>	3.32	3.02	1.42	1.29	0	0	0	0	33.75	32.41	25.71	25.33
N <sub>3</sub>	2.99	2.55	1.27	1.08	0	0	0	0	30.79	29.42	15.65	16.40
N <sub>4</sub>	2.68	2.58	1.09	1.07	0	0.08	0	0.03	38.50	36.66	13.34	12.50
H <sub>N1</sub>	2.00		0.77		0		0		23.88		21.46	
H <sub>N2-N4</sub>	1.67		0.58		0		0		17.94		15.46	
Otitis		Febrile pharyngitis		Whooping cough		Measles		Child-days				
i	o	i	o	i	o	i	o	i	o	i	o	
0.54	0.55	0.97	1.05	0	0	0	0	1,658		2,008		
0.23	0.21	0.82	0.74	0.16	0.13	0.16	0.16	3,056		3,770		
0.29	0.27	0.39	0.35	0.05	0.08	0.05	0.06	3,846		4,821		
0.18	0.18	0.43	0.42	0.20	0.18	0.10	0.09	3,966		4,478		
0.03		0.47		0		0.15		3,418				
0.16		0.44		0.01		0.04		7,055				
0.13		0.34		0		0		4,451				
0.03		0.29		0		0		3,796				
0.08	0.10	0.45	0.56	0.04	0.07	0.16	0.17	2,447		3,028		
0.21	0.18	0.21	0.23	0.11	0.11	0.37	0.32	3,796		4,434		
0.07	0.08	0.34	0.30	0	0.03	0.34	0.28	2,907		3,610		
0.03	0.03	0.22	0.28	0	0	0.25	0.20	3,208		3,920		
0.06		0.62		0.12		0.03		3,392				
0.06		0.40		0.03		0.06		7,051				

table 5, which includes both the infection indices and the number of child-days on which they were calculated.

It now seems possible to draw certain general conclusions from the values given in the table. As regards the institution groups it is immediately clear that the indices calculated for the institution time (i) are in some instances slightly higher than the values referring to the observation time (o), in some instances, on the other hand, rather lower, and that the differences throughout are relatively insignificant. The number of o-days, however, exceeds the number of i-days by about 15 per cent, and this excess observation time corresponds to times when the children were mostly at home. If, accordingly, a somewhat lower morbidity occurred among the children at certain periods when they were mostly at home, this has apparently been compensated for by a higher morbidity during other such periods. It should be remembered with respect to this that children often left the institution in connection with a period of illness, and that this "last illness period" is often included in the o-calculations but not, on the other hand, in the i-calculations. For reasons which were mentioned earlier, however, the latter have been accorded greater significance.

Concerning the morbidity values found, it can in general be said that those for the day nursery groups are on a very high level, especially those for group D<sub>2</sub> (2 year olds). The fever index here is about twice, and the nasal discharge index about three times as high as in the corresponding home groups. The nursery school children show a generally lower morbidity than the day nursery children, but their morbidity also exceeds that of the corresponding home groups.

Hospitalization was carried out to some extent in the day nursery group (1.1—3.5 per cent of the observation time of these children is composed of hospital days), and in a considerably smaller degree among the home children (0—0.9 per cent). The figures for "fever in hospital" are very small, but follow for the most part, the corresponding hospitalization figures. There were some cases of whooping cough in the institution group; measles was more frequent. Table 6 shows the occurrence of specific infections in the material.

Measles and whooping cough cases have, as is seen, been quite numerous, for which reason their significance to the indices for

**Table 6. Occurrence of Specific Infectious Diseases  
in the Different Groups**

**Investigation I**

Group no.	Whooping cough		Measles		Mumps		Chickenpox	
	D	H <sub>D</sub>	D	H <sub>D</sub>	D	H <sub>D</sub>	D	H <sub>D</sub>
1	—	—	—	5	—	—	1	—
2	5	1	6	3	—	1	—	1
3	4	—	3	3	—	1	—	—
4	8	—	4	—	2	—	—	1
	N	H <sub>N</sub>	N	H <sub>N</sub>	N	H <sub>N</sub>	N	H <sub>N</sub>
1	2	4	5	1	1	1	—	—
2	5	2	14	3	2	8	—	—
3	1		10		5			
4	—		8		—		1	—

D = day nursery groups.

N = nursery school groups.

H<sub>D</sub> and H<sub>N</sub> = home groups.

fever, nasal discharge and cough cannot be ignored. To that there must be added the fact that their distribution in the different groups is uneven. This partly forms the basis for the calculations of the net morbidity, made in order to obtain a better picture of the occurrence of true respiratory infections. (The cases of mumps and chickenpox, on the other hand, were of little significance in this respect.)

*Net morbidity*

As has been mentioned earlier, the recording of the net morbidity differed from the recording of the gross morbidity not only through the corrections made for the above-named specific infections, but also through the exclusion of certain children from the calculations for nasal discharge. There were eight of these, 4 in the day nursery (two in group D<sub>2</sub>, two siblings in group D<sub>4</sub>), 2 in the nursery school (siblings, in group N<sub>1</sub> and N<sub>2</sub>, respectively), and 2 among the home children (siblings in group H<sub>D3</sub>). They all had an almost perpetual, serous nasal discharge. The two children in group D<sub>2</sub> also had

Table 7. Net Infection Indices

## Investigation I

Group	Fever		Nasal dis-charge	Cough	Diarrhoea	Vo-miting	Otitis	Febrile pharyngitis	No. of child-days													
	38° C	39° C							1	2	3	4	5	6	7	8	col. 5-8	without reductions	with reductions for calculations in	col. 1&2	col. 3	col. 4
																	col. 5-8	without reductions	with reductions for calculations in	col. 1&2	col. 3	col. 4
D <sub>1</sub>	3.80	1.51	43.18	26.18	1.57	1.03	0.54	0.97	1,658	1,656	1,658	1,658										
D <sub>2</sub>	3.25	1.44	61.25	33.32	0.87	0.27	0.23	0.84	2,986	2,986	2,542	2,245										
D <sub>3</sub>	2.05	0.66	46.90	18.89	0.13	0.34	0.29	0.39	3,808	3,808	3,808	3,202										
D <sub>4</sub>	1.74	0.77	43.30	18.88	0.03	0.31	0.18	0.43	3,920	3,916	3,464	2,849										
D <sub>1-4</sub>	2.48	1.00	48.72	23.34	0.47	0.41	0.27	0.59														
H <sub>D1</sub>	2.21	0.63	23.63	13.35	0.60	0.39	0.03	0.48	3,348	3,348	3,348	3,348										
H <sub>D2</sub>	1.76	0.66	21.29	12.48	0.33	0.23	0.16	0.44	7,013	7,009	7,013	6,857										
H <sub>D3</sub>	1.48	0.47	15.88	16.67	0.36	0.34	0.13	0.36	4,451	4,447	3,993	4,066										
H <sub>D4</sub>	1.24	0.32	21.07	9.92	0.13	0.24	0.03	0.32	3,796	3,790	3,796	3,338										
H <sub>D1-4</sub>	1.57	0.49	19.87	13.08	0.31	0.29	0.09	0.38														
N <sub>1</sub>	2.38	0.42	42.73	24.30	0	0.50	0.08	0.46	2,392	2,391	2,214	1,395										
N <sub>2</sub>	1.20	0.47	31.09	18.76	0.31	0.75	0.19	0.22	3,600	3,596	3,419	2,878										
N <sub>3</sub>	1.34	0.43	29.71	13.13	0.11	0.29	0.07	0.36	2,767	2,761	2,767	1,958										
N <sub>4</sub>	1.45	0.56	37.73	10.65	0.16	0.29	0.03	0.23	3,096	3,096	3,096	2,921										
N <sub>2-4</sub>	1.32	0.42	32.89	14.28	0.20	0.46	0.11	0.26	9,463	9,453	9,282	7,757										
N <sub>1-4</sub>	1.87	0.42	34.88	16.30	0.16	0.47	0.10	0.30														
H <sub>N1</sub>	1.75	0.53	23.56	14.44	0	0.03	0.06	0.62	3,378	3,376	3,378	2,811										
H <sub>N2-4</sub>	1.43	0.49	17.79	14.12	0.06	0.26	0.06	0.40	7,004	6,990	7,004	6,791										
H <sub>N1-4</sub>	1.49	0.50	18.95	14.18	0.05	0.21	0.06	0.44														

For institution groups, calculations are based on institution time.

eczema and asthmatic bronchitis, respectively; the siblings in group N<sub>1</sub> and N<sub>2</sub> had eczema and those in group H<sub>D3</sub> often had urticaria.

Table 7 shows the results of the calculations of the net morbidity, both the values for individual groups, and the total values for the whole day nursery and nursery school materials as well as for the corresponding home materials. The total values mentioned are weighed means, in the calculation of which the average numbers of the institution groups' unreduced i-days per period have served as the weights (in future denoted as the standard weights of the groups). For groups N<sub>2</sub>, N<sub>3</sub>, and N<sub>4</sub>,

Table 8. Comparison of Net Infection Indices for Institution and Home Groups.

Investigation I      Net Indices for Fever, Nasal Discharge and Otitis

Group no.	Material		Diff. D-H <sub>D</sub>	D. f.	Variance ratio	P
	D	H <sub>D</sub>				
F e v e r						
1	3.80	2.21	+ 1.59	1/33	1.82	0.2—0.05
2	3.25	1.76	+ 1.49	1/57	5.51	0.05—0.01
3	2.05	1.48	+ 0.62	1/51	0.85	> 0.2
4	1.74	1.24	+ 0.50	1/43	0.78	> 0.2
1—4	2.48	1.57	+ 0.91	1/190	6.80	≤ 0.01
	N	H <sub>N</sub>	N—H <sub>N</sub>			
1	2.38	1.75	+ 0.63	1/39	0.52	> 0.2
2—4	1.32	1.43	— 0.11	1/113	0.11	> 0.2
1—4	1.87	1.49	+ 0.38	1/154	1.63	> 0.2
N a s a l D i s c h a r g e						
	D	H <sub>D</sub>	D—H <sub>D</sub>			
1	43.18	23.63	+ 19.55	1/33	10.43	0.01—0.001
2	61.25	21.29	+ 39.96	1/55	62.37	< 0.001
3	46.90	15.88	+ 31.02	1/49	28.29	< 0.001
4	43.30	21.07	+ 22.23	1/41	16.41	< 0.001
1—4	48.72	19.87	+ 28.85	1/184	102.64	< 0.001
	N	H <sub>N</sub>	N—H <sub>N</sub>			
1	42.73	23.56	+ 19.17	1/38	10.27	0.01—0.001
2—4	32.89	17.79	+ 15.10	1/112	13.97	< 0.001
1—4	34.88	18.95	+ 15.93	1/152	22.12	< 0.001
O t i t i s						
	D	H <sub>D</sub>	D—H <sub>D</sub>			
1—4	0.27	0.09	+ 0.18	1/190	8.74	0.01—0.001
	N	H <sub>N</sub>	N—H <sub>N</sub>			
1—4	0.10	0.06	+ 0.04	1/154	0.89	> 0.2

D = day nursery groups

N = nursery school groups

H<sub>D</sub> and H<sub>N</sub> = home groups

which are approximately uniform as regards age, arithmetical means have been calculated, and are shown under N<sub>2—4</sub>.

For the institution groups the table includes only the values calculated for the institution time; the values for the observation time, which are not included here, deviate little from these.

A comparison with table 5, showing the gross morbidity, reveals that the indices for fever are here considerably lower for the groups where measles had been a common occurrence (principally nursery school groups N<sub>1</sub>—N<sub>4</sub>). The indices for nasal discharge have only been slightly influenced except in the groups where *two* children were excluded because of suspected allergic rhinitis (D<sub>2</sub>, D<sub>4</sub> and H<sub>D3</sub>). The values for cough have diminished mainly in the groups where whooping cough was relatively common (D<sub>2</sub>, D<sub>4</sub>, N<sub>2</sub> and H<sub>N1</sub>). Otherwise, the indices are for the most part unchanged.

A comparison between the values for the *day nursery material* as a whole (D<sub>1-4</sub>) and the values for the corresponding home material (H<sub>D1-4</sub>) shows a considerably higher morbidity with respect to respiratory infections among the day nursery children than among the home children. The difference is manifest in all respects recorded, and as is clear from table 8 it is statistically probable for fever of 38° C, significant in the case of nasal discharge and very probable for otitis. The probability value found for fever should, in itself, in accordance with the definition, justify the expression "very probable difference", but in view of the fact that firstly, the individual indices for each child could not be regarded as having a normal distribution around their means, and secondly, in view of the general reservations made earlier on the question of the calculation of the morbidity index, the criteria of significance have been judged rather more stringently than is implied by the scheme on page 28.

In the individual day nursery groups the analysis with regard to nasal discharge shows throughout a significant or very probable excess over the corresponding home groups. As regards fever, the difference can be described as probable only for group D<sub>2</sub>.

Concerning diarrhoea and vomiting it can be observed that although these symptoms, like the others, were in the main commoner among day nursery than home group children, they did not occur in the former group to any large extent. No true nosocomial dyspepsias occurred in the institution during the investigation.

The *nursery school material* also showed a clear preponderance in respect of the characteristics recorded, in comparison with their corresponding home material, although the difference was not so great as that shown by the day nursery children. The indices were higher for the nursery school children than for the home group

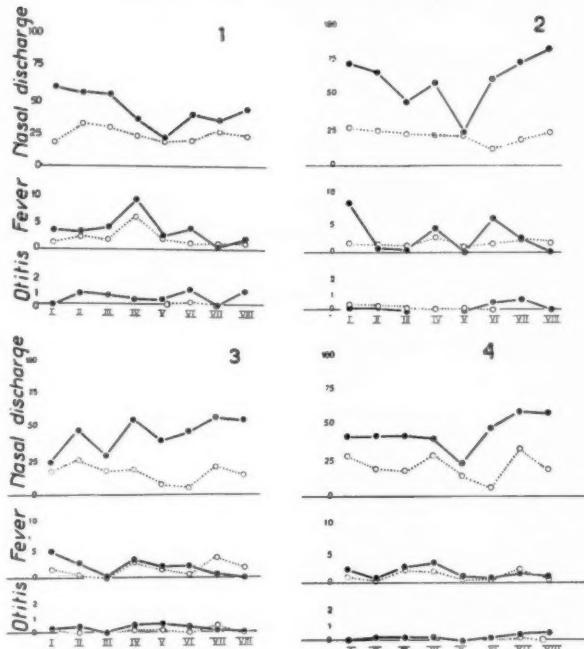
**Table 9. The Material in the Institution Groups per Period**  
**Investigation I**

Group	Period							
	I	II	III	IV	V	VI	VII	VIII
D <sub>1</sub>	9 236	9 253	10 279	11 223	10 224	6 186	8 161	7 96
D <sub>2</sub>	17 474	15 434	13 380	13 374	13 265	18 423	16 447	13 189
D <sub>3</sub>	23 657	19 570	19 464	17 397	15 360	20 561	19 526	17 273
D <sub>4</sub>	21 579	20 569	18 500	20 529	19 462	18 558	19 524	14 199
N <sub>1</sub>	17 492	16 476	8 16	14 334	14 332	13 375	13 367	—
N <sub>2</sub>	21 651	21 613	18 36	20 440	23 547	23 688	23 625	—
N <sub>3</sub>	20 606	19 569	18 36	20 417	15 297	15 437	15 405	—
N <sub>4</sub>	21 604	19 540	18 35	22 495	20 482	17 508	16 432	—

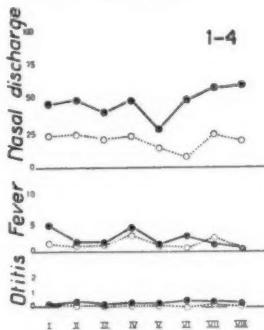
**Table 10. The Material in the Home Groups per Period**  
**Investigation I**

Group	Period							
	I	II	III	IV	V	VI	VII	VIII
H <sub>D1</sub>	15 448	15 450	15 465	15 463	15 382	15 449	15 437	15 254
H <sub>D2</sub>	32 975	32 960	32 978	31 961	31 856	31 961	30 870	29 452
H <sub>D3</sub>	20 620	20 600	20 606	19 589	19 532	20 620	20 595	17 289
H <sub>D4</sub>	17 527	17 510	17 510	16 496	16 448	17 510	17 510	17 285
H <sub>N1</sub>	16 496	16 480	16 496	16 496	16 448	16 482	16 480	—
H <sub>N2-4</sub>	34 1,020	34 1,020	34 1,054	34 1,054	34 920	33 1,023	32 913	—

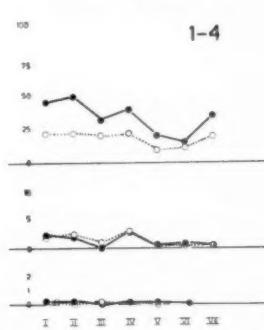
### Day nursery and home groups



### Day nursery and home materials



### Nursery school and home materials



*Fig. 2. Graphical representation of net infection indices obtained for nasal discharge, fever and otitis during various periods. —— denotes institution groups. ○ ···○ denotes home groups.*

in all respects except febrile pharyngitis. It was found, however, that the differences for fever and otitis could have been wholly due to chance, while the difference for nasal discharge is statistically significant.

#### *Variations in the morbidity*

The variations in the incidence of respiratory infections in different stages of the investigation were studied by calculating the indices for fever, nasal discharge and otitis in the various groups for each of the periods separately (according to the division into periods shown on page 48). Mean values for the whole day nursery and nursery school, as well as for the corresponding home materials, were also calculated by standard weighing (with the various groups' standard weights, page 53). The calculations were based on the net morbidity and, in the case of the institution groups, on the institution time. The size of the material during the different periods, expressed in terms of the number of children and the corresponding number of child-days, will be seen in tables 9 and 10, while fig. 2 provides a representation of the morbidity values found.

It would seem, from the curves, that there are no very decided tendencies which are common to the various sections of the material and accordingly could be a reflection of widespread changes in the general incidence of respiratory infections. Especially in the different groups of home material, the variations from one period to another are remarkably small. Some groups, especially in the day nursery, are, it is true, characterised by lower morbidity in periods V and VI (Feb. 15—Apr. 14) than in earlier and later stages of the investigation time, but the tendency in this direction is not general.

A comparison of the curves and tables 9 and 10 suggests that the correlation between unusual morbidity and an unusual number of child-days in a group did not occur to such an extent as to cause obvious disturbance in the basis for the calculation of the morbidity index for the whole investigation time (cf. page 27).

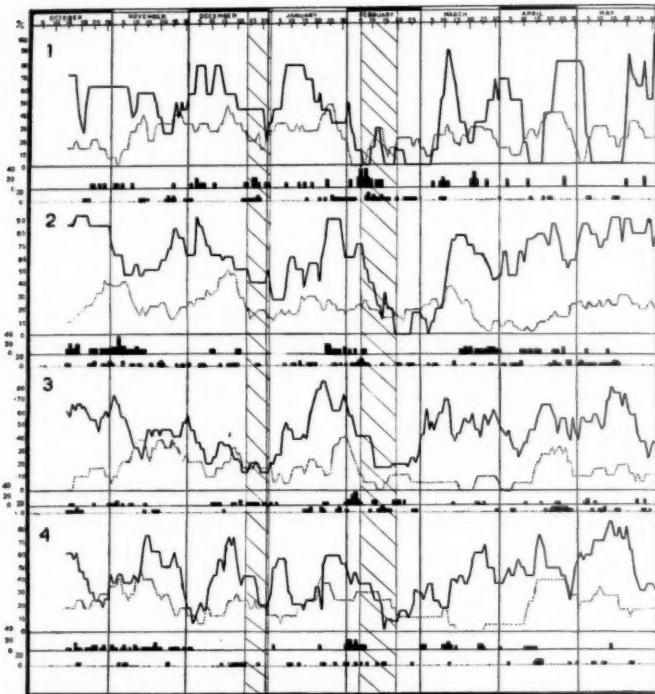
The relatively small and indefinite variations in the morbidity are quite surprising, especially in view of the fact that an epidemic of influenza A was raging in Sweden during one stage of the investigation. This epidemic has been described by Löfström (1949). Ac-

cording to his paper, the frequency figures, which were in general comparatively high, showed a culmination in the environments of Stockholm in the last half of January and the beginning of February 1947. (During the preceding and following fortnights the number of cases occurring was considerably smaller.) No special figures are available for the population of the island where the investigation was carried out, but it is certain that the epidemic here was also widespread. During this time it was very common, on visiting a home, to find the child's parents confined to bed with influenza. It is striking that the morbidity among the children, as is clear from the diagrams, did not increase to any particular extent during this period (period IV), either among the institution or the home groups. This tallies with the fact that no clinically typical cases of influenza among the children could be observed. Admittedly, it is probably almost impossible, as we see for instance, from Adam's, Thigpen's and Rickard's investigation (1944), to differentiate mild cases of influenza from common pharyngitis in children even during an influenza epidemic. The slight rise in the index curve for fever that is apparent in most of the groups during period IV might, however, be connected with the occurrence of influenza among the children also. It seems probable, however, that the children examined during this influenza epidemic were affected to a considerably smaller extent than the adults.

The curves shown in figs. 3 and 4 give a more detailed picture of the variations in the morbidity in the various groups. They demonstrate the number of children with fever, and those with nasal discharge, for each day, expressed in percentage of the number of children included in the calculations. The calculations are based on the net morbidity, and in the case of institution children on the institution time.

Period III, for the nursery school groups is an exception to this. As the nursery school was mainly closed during this period the institution time, as previously mentioned, was reckoned only for the two days it was open. The values for the remaining part of the period, which, for the sake of continuity, are indicated in fig. 4, have therefore been calculated on the observation time. As the values for the morbidity based on these two time concepts showed no great divergences, this should be of little importance.

The curves illustrate how relatively little the morbidity varied for *the home groups* during the investigation. The percentage



*Fig. 3.* Graphical representation of the daily variations in the net morbidity for the day nursery groups and the corresponding home groups.

Solid lines denote nasal discharge in day nursery groups

Dotted \* \* \* \* \* home \*

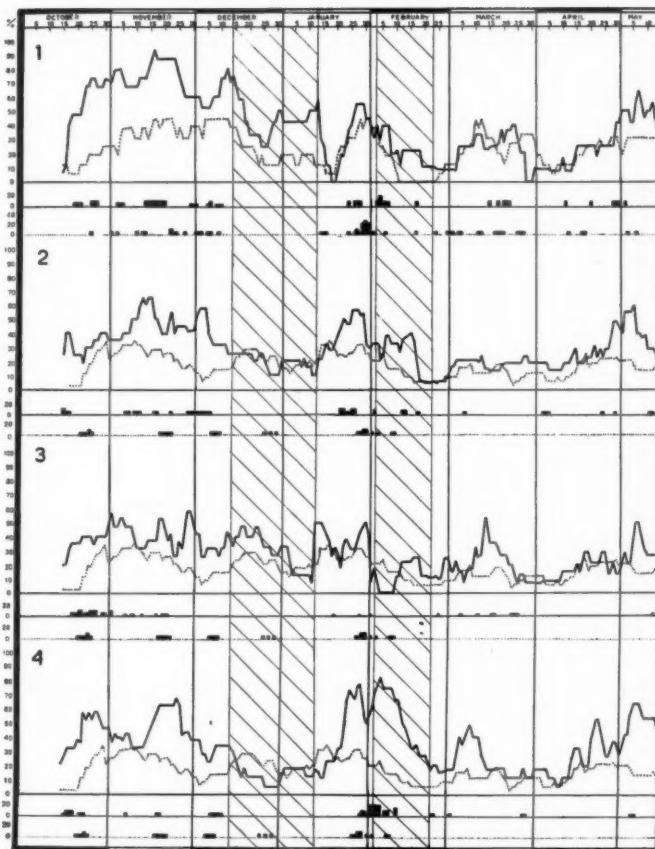
Blocks on solid lines denote fever in day nursery groups

\* \* dotted \* \* \* \* home \*

Shaded areas = day nursery closed.

figures for nasal discharge keep fairly close to the mean value of about 20, with transient fluctuations in both directions. The fever days are fairly evenly spread over the whole period, perhaps occurring in greater numbers around the end of January and beginning of February. There do not seem to be any appreciable differences in the course of the curves for the different age groups.

The situation is quite different with the *day nursery children* (fig. 3). Here there are waves of infection, accompanied by accumulation



*Fig. 4.* Graphical representation of the daily variations in the net morbidity for the nursery school groups and the corresponding home groups.

Solid lines denote nasal discharge in nursery school groups.

Dotted \* \* \* \* \* home \*

Blocks on solid lines denote fever in nursery school groups.

\* \* dotted \* \* \* \* home \*

Shaded areas = nursery school closed.

of fever cases and rises in the frequency of nasal discharge. The occurrence of nasal discharge, because of the commonness of this symptom, ought to be especially suitable for demonstrating the situation with regard to infection in the groups. There seem to be

certain differences, in this respect, between the various age groups. Thus, the curve for group D<sub>2</sub> (2 year olds) suggests that the children in this group were almost always more or less infected; the waves of infection have a protracted course and the frequency of nasal discharge approaches the level of the home group only on one or two occasions. On the other hand, the curve for group D<sub>4</sub> (5—7 year olds), shows that considerable increases in the morbidity did, admittedly, often occur in this group also, but these infection waves were of relatively short duration, the sick-rate soon dropping towards that shown by the home group. Between these two extremes, group D<sub>3</sub> (4 year olds) seems to hold an intermediate position. Finally the curve for group D<sub>1</sub> (one year olds), which, due to the small number of children, is more uneven in its course than the others, has somewhat the same appearance as the curve for group D<sub>4</sub>, with waves of infection of relatively short duration. The peaks in the former group, however, tend to reach a higher level.

It looks as though we can assume that these differences in the curves are largely due to various circumstances connected with resistance and the spread of infection, which, in their turn, may be related to the age of the children. This question will be dealt with more fully later.

Finally, the curves for *the nursery school groups* (fig. 4) for long periods follow a course similar to those for the corresponding home groups. A number of waves of infection apparently occurred, however, but generally they were of short duration. An exception to this is group N<sub>1</sub> where, in the autumn, respiratory infections were exceedingly common.

The shaded parts of the curves show the periods when the institution was closed for the Christmas holidays and for the measles epidemic. It would appear, in the case of the day nursery, that for the days immediately following this latter, longer, period the incidence of nasal discharge was lower than what was otherwise generally the case.

#### *Complications observed*

Of the illnesses encountered which could be classified as complications of the respiratory group of infections, otitis has been mentioned earlier. Besides this, sinusitis was diagnosed, eleven cases among the day nursery children, and four cases among the nursery

school children as against one in the home group. Bronchitis or bronchopneumonia accompanied by pyrexia was diagnosed in eight day nursery children, three nursery school children and four home group children. Both with regard to sinusitis and to bronchitis and bronchopneumonia, however, the diagnostic possibilities were limited, as I stated before, and the number of cases of these diseases was therefore, in all probability, much larger in actual fact.

Among the day nursery children two cases of acute nephritis occurred in connection with severe infections accompanied by otitis. In the home material one case of pharyngotonsillitis was complicated with generalized sepsis (bronchopneumonia, pleurisy, otitis) for which the child stayed in hospital for 43 days (this explains the relatively high index for hospitalization for group-H<sub>D</sub>, table 5).

## CHAPTER IV

### *Investigation II*

This investigation aimed at analysing the extent to which the morbidity among children would be affected by the principle of avoiding admitting to a day nursery children with signs of respiratory infections. This principle was adopted in one half of a modern nursery, while the other half was run according to current practice and served as a control. The investigation was concerned with day nursery children aged three months to six years.

#### *Institution investigated*

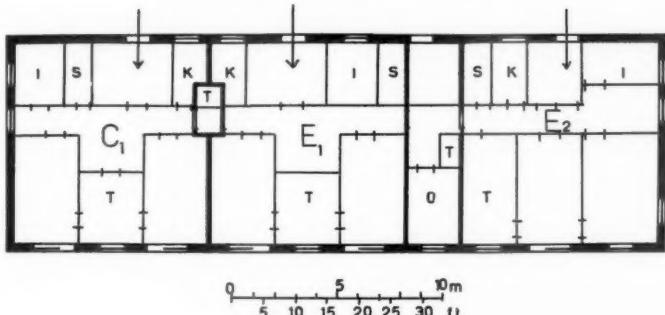
A different day nursery was chosen for this investigation from the one used in Investigation I. It is situated in one of Stockholm's outer suburbs. The buildings in this area consist mainly of factories in the fine engineering industry and dwelling-houses containing one and two roomed flats, nearly all built in the last decade. The parents of the day nursery children are, for the most part, factory workers or office workers. Thus the socio-economic standard, like the general level of housing, is somewhat lower than on the island where Investigation I was undertaken.

#### *Premises*

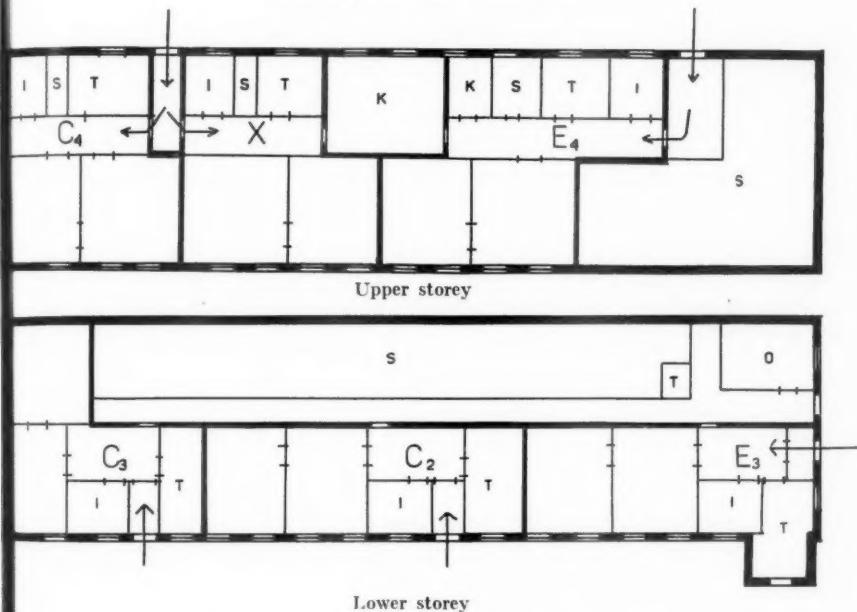
This day nursery had just been built at the beginning of the investigation. It consists of two separate buildings, a small one-storey building for the youngest children and a larger two-storey building for the older children. Plans of the buildings are given in fig. 5.

Of the nine departments, eight were used for the investigation. Their designations, number of places and age limits, and also the space available, are shown in table 11. In the remaining depart-

**Building for young children**



**Building for older children**



*Fig. 5. Plans of the Day Nursery studied in Investigation II.*

E<sub>1, 2, 3, 4</sub>, C<sub>1, 2, 3, 4</sub> and X = various departments. O = superintendent's office. T = toilet rooms. K = kitchens. S = storage rooms, staff quarters, and so on. I = isolation rooms. The same scale applies to all 3 plans.

**Table 11. Character and Details of the Various Departments  
Investigation II**

Character		Age	No. of places	Floor area	
				m <sup>2</sup>	sq. feet
E <sub>1</sub>	Experiment group	3 mths.—1 yr.	10	30.0	323.0
E <sub>2</sub>	do.	1—2 yrs.	10	32.5	349.9
E <sub>3</sub>	do.	2—3½ yrs.	12	40.0	430.6
E <sub>4</sub>	do.	3½—6 yrs.	15	46.5	500.6
C <sub>1</sub>	Control group	3 mths.—1 yr.	10	30.0	323.0
C <sub>2</sub>	do.	1—2 yrs.	10	37.5	403.7
C <sub>3</sub>	do.	2—3½ yrs.	12	40.6	437.1
C <sub>4</sub>	do.	3½—6 yrs.	15	46.0	495.2

ment, marked X in the diagram, the children over six years old who were not included in the investigation were housed.

As is clear from fig. 5 the day nursery is constructed with an eye to the provision of, among other things, adequate isolation between the different departments. They all have separate entrances with the exception of department C<sub>4</sub>, which has a common entrance with department X. Throughout the investigation the doors between departments E<sub>1</sub> and C<sub>1</sub> were kept locked.

A couple of play-grounds and a balcony attached to the smaller building also form part of the nursery. Central heating is installed.

#### *Staff*

During the investigation the staff of the day nursery consisted of two superintendents, two nursery nurses for each of the groups E<sub>1</sub>, E<sub>2</sub>, E<sub>3</sub>, C<sub>1</sub>, C<sub>2</sub>, and C<sub>3</sub>, a nursery school teacher and a nursery nurse for each of groups E<sub>4</sub> and C<sub>4</sub> besides a nursery nurse shared by groups E<sub>1</sub> and E<sub>2</sub> (plus one nursery school teacher and a pupil in group X). Four people were employed in the kitchen and laundry. The total staff, accordingly, consisted of 25 persons, apart from part-time cleaners and a porter. When staff moves were necessary through illness etc. the personnel from one of the E groups was allowed to work with one of the other groups within the same material, but not with the C groups, and vice versa.

Table 12. Age and Social Conditions

Comparison between Experiment and Control Groups

Investigation II

Date survey made	Group	No. of children	Mean age in months	Mean no. of members in family			Mean no. of rooms in home			Socio-economic group	
				Adults	Children		Bed & living rooms	Hall or dining-recess	Kitchen		
					All ages	School age					
Dec. 1 1947	E <sub>1</sub>	6	9.7	2.2	1.0	0	1.3	0.2	1.0	2.3	
	E <sub>2</sub>	7	18.0	2.3	1.1	0.1	1.3	0.1	1.0	2.4	
	E <sub>3</sub>	9	33.0	2.4	1.0	0	1.7	0.1	0.9	2.4	
	E <sub>4</sub>	6	47.0	2.0	1.7	0.7	1.5	0.2	1.0	2.8	
	E <sub>1-4</sub>	28	27.3	2.2	1.2	0.2	1.5	0.1	1.0	2.5	
	C <sub>1</sub>	6	6.5	2.2	1.2	0	1.5	0.3	1.0	2.8	
	C <sub>2</sub>	8	19.2	2.1	1.7	0.2	1.6	0.4	1.0	2.5	
	C <sub>3</sub>	10	34.2	1.9	1.8	0.4	1.7	0.3	1.0	2.4	
	C <sub>4</sub>	12	52.5	2.6	1.8	0.3	2.0	0.3	1.0	2.6	
	C <sub>1-4</sub>	36	28.4	2.2	1.6	0.2	1.7	0.3	1.0	2.6	
Mar. 1 1948	E <sub>1</sub>	6	11.7	2.2	1.0	0	1.5	0	1.0	2.3	
	E <sub>2</sub>	8	20.1	2.1	1.2	0.1	1.2	0.1	0.9	2.4	
	E <sub>3</sub>	8	36.6	2.4	1.0	0	1.5	0.1	0.9	2.4	
	E <sub>4</sub>	12	54.8	1.9	1.7	0.5	1.3	0.1	1.0	2.8	
	E <sub>1-4</sub>	34	34.7	2.1	1.3	0.2	1.4	0.1	1.0	2.5	
	C <sub>1</sub>	6	9.5	2.2	1.2	0	1.5	0.3	1.0	2.8	
	C <sub>2</sub>	10	20.0	2.1	1.6	0.3	1.4	0.3	0.9	2.4	
	C <sub>3</sub>	10	35.4	1.9	1.6	0.4	1.7	0.2	1.0	2.4	
	C <sub>4</sub>	13	54.1	2.3	1.8	0.5	1.8	0.4	1.0	2.5	
	C <sub>1-4</sub>	39	33.8	2.1	1.6	0.3	1.6	0.3	1.0	2.5	
June 1 1948	E <sub>1</sub>	8	12.4	2.1	1.0	0	1.5	0	1.0	2.1	
	E <sub>2</sub>	8	21.4	2.2	1.1	0	1.4	0.1	1.0	2.2	
	E <sub>3</sub>	13	38.2	2.2	1.1	0	1.3	0.1	1.0	2.5	
	E <sub>4</sub>	11	53.8	2.0	1.3	0.3	1.6	0.1	1.0	2.5	
	E <sub>1-4</sub>	40	34.0	2.1	1.1	0.1	1.4	0.1	1.0	2.4	
	C <sub>1</sub>	8	12.7	2.1	1.1	0	1.4	0.5	1.0	2.6	
	C <sub>2</sub>	8	21.7	2.1	1.9	0.4	1.5	0.5	1.0	2.5	
	C <sub>3</sub>	12	38.7	2.0	1.5	0.3	1.5	0.3	1.0	2.5	
	C <sub>4</sub>	10	59.7	2.3	1.7	0.4	2.1	0.1	1.0	2.7	
	C <sub>1-4</sub>	38	35.9	2.1	1.6	0.3	1.6	0.3	1.0	2.6	

### *Daily routine of the nursery*

The day nursery is open from 6.30 a. m. to 6.0 p. m. (on Saturday 2.0 p. m.). In the morning all children are received into their proper departments, and there is no contact inside the building between children belonging to different groups. The daily routine coincides otherwise, in the main, with that described earlier for Investigation I. Owing to the fact that the staff is larger, however, the children at this nursery have more opportunity of playing outside.

### *Method of the investigation*

At the beginning of the investigation, in November 1947, the children enrolled were classified on the same principles as described for Investigation I, so as to produce two comparable series, and arranged so that group E<sub>1</sub>, as far as possible, corresponded to group C<sub>1</sub>, E<sub>2</sub> to C<sub>2</sub>, E<sub>3</sub> to C<sub>3</sub> and E<sub>4</sub> to C<sub>4</sub>. In placing children enrolled later an attempt was made to maintain the balance between the groups. The characteristics of the different groups at the beginning, middle and end of the investigation are shown in table 12. In the calculations of the joined means E<sub>1-4</sub> and C<sub>1-4</sub>, the number of children in the E groups have been used as the weights. Concerning the distribution on boys and girls, what was said on the subject in connection with Investigation I applies here.

It seems clear from the tables that in general the correlation between the groups to be compared is satisfactory.

Information concerning the investigation, its aims and methods, was conveyed to the parents by post and at a parents' meeting. In this investigation also, co-operation with the homes proved easy to achieve, although these were spread over a much larger area than in Investigation I. The same principles for the observation of the children in the day nursery and in the home were applied as indicated earlier for the institution children in Investigation I. An ear, nose and throat specialist examined the day nursery children on two occasions and attended any cases of illness in his special field. Adenoidectomy was performed on 16 children (6 among the E groups, 10 among the C groups).

For the purposes of the investigation the following principles were applied to the respective groups.

### *Experiment groups*

Every child who belonged to the E groups was inspected on arrival in the morning by myself or one of my two assistants, both health visitors (two of us were present every morning). This inspection took place in the presence of the parents and before the child came in contact with the others. We accepted only children who apparently, and according to the parents, were free from signs of respiratory infections. If there were any such symptoms, however slight, the parents were asked to take the child back home and care for it there until it could be readmitted.

To enable such a procedure to be carried out without too troublesome complications I had at my disposal two full-time nursery nurses plus occasional help, when necessary, to look after the sick children at home. They were asked to take charge when the symptoms were so slight that the child, in the normal way, would have been accepted, and of course only when the mother wished it. In many cases the mother preferred to stay away from work herself.

### *Control groups*

The children belonging to the C groups were admitted to the extent which is customary in day nurseries in the general course of events. The persons carrying out the investigation effected no changes here, questions of this nature being decided by the day nursery's own staff. The latter followed the orders of the day nursery's physician.

### *Calculations and results*

#### *Investigation time*

The investigation was commenced in the early part of November 1947. Only towards the end of this month, however, were all the groups organised. The investigation period was therefore counted from Nov. 3 for groups E<sub>1</sub>, E<sub>2</sub>, C<sub>1</sub>, and C<sub>2</sub>, from Nov. 10. for groups E<sub>3</sub> and C<sub>3</sub> and from Nov. 20 for groups E<sub>4</sub> and C<sub>4</sub>. The observations for all the groups were concluded on June 15, 1948. The investigation has been divided into periods of one calendar month's duration. The day nursery was closed for the Christmas holidays between 24th and 28th December, 1947.

*Scope of the material*

Investigation II embraced 145 children. Their distribution among the different groups is shown in table 13.

Table 13. Total Number of Children in the Various Groups  
Investigation II

	E <sub>1</sub>	E <sub>2</sub>	E <sub>3</sub>	E <sub>4</sub>	C <sub>1</sub>	C <sub>2</sub>	C <sub>3</sub>	C <sub>4</sub>
Boys.....	7	12	14	10	6	9	12	11
Girls.....	10	5	11	14	6	4	11	11
Boys + Girls ...	17	17	25	24	12	13	23	22

Table 14. Gross Infection Indices  
Investigation II

Group	F e v e r				H o s p i t a l i z e d				Nasal discharge		Cough	
	38° C		39° C		Total		With fever		i	o	i	o
	i	o	i	o	i	o	i	o	i	o	i	o
E <sub>1</sub>	2.43	2.40	0.64	0.64	0	0	0	0	24.57	25.37	17.57	18.23
E <sub>2</sub>	3.97	4.10	2.20	2.05	0.85	0.76	0.24	0.22	32.48	34.41	21.43	24.38
E <sub>3</sub>	0.88	1.19	0.33	0.62	0	0	0	0	21.57	23.34	9.91	10.66
E <sub>4</sub>	0.70	0.74	0.35	0.41	0.09	0.08	0	0	21.04	21.53	14.35	14.56
C <sub>1</sub>	2.55	3.14	1.05	1.19	0.92	1.38	0	0	35.86	35.16	21.20	21.01
C <sub>2</sub>	2.39	2.33	1.12	1.09	0.74	0.72	0.05	0.05	69.75	68.58	26.53	26.09
C <sub>3</sub>	1.02	0.99	0.31	0.30	1.55	1.51	0	0	55.17	54.76	30.82	30.13
C <sub>4</sub>	1.17	1.35	0.45	0.13	0.67	0.64	0.09	0.08	35.56	34.97	7.98	10.33

Otitis		Febrile pharyngitis		Whooping cough		Child-days	
		i	o	i	o	i	o
0.07	0.07	1.14	1.13	0	0	1,400	1,415
0.18	0.22	1.22	1.24	0	0.05	1,638	1,854
0	0	0.50	0.57	0	0	1,817	1,932
0.13	0.12	0.26	0.29	0	0	2,300	2,438
0	0.06	0.85	1.01	0	0	1,528	1,590
0.11	0.10	1.06	1.04	0.05	0.05	1,881	1,932
0.27	0.26	0.44	0.43	0.13	0.13	2,255	2,323
0.27	0.25	0.18	0.25	0	0.04	2,230	2,362

Owing to moves (which mainly occurred within, but not between the E and C materials), one child is in some cases a member of two groups. A girl in each of groups  $E_4$  and  $C_2$  is included only in the calculations based on the observation time. The number of children included in the calculations for the institution time is therefore 143.

#### *Gross morbidity*

The calculation of the gross morbidity was made on the same principles as in Investigation I. The result is shown in table 14.

It is clear from the table that the differences between the indices obtained for the institution time (i) and for the observation time (o) are in the main small, also that the infection indices for nasal discharge and to a certain extent also for cough, show higher values for groups  $C_{1-4}$  than for groups  $E_{1-4}$ , while in other respects the relations are indefinite. Hospitalization occurred only to a small extent.

Only a few cases of the specific infections occurred. There was one case of whooping cough in each of groups  $E_2$ ,  $C_2$  and  $C_4$ , plus three cases in group  $C_3$ ; four cases of mumps in group  $C_4$ , and one case in group  $E_4$ , and one case of chickenpox in group  $C_3$ ; measles did not occur.

#### *Net morbidity*

There were some children in this series also whose nasal discharge was probably largely of an allergic nature. There were seven of these, one in group  $E_2$  (eczema, allergic heredity), one in group  $E_3$  (ditto), two siblings in groups  $C_2$  and  $C_4$  (ditto), two siblings in groups  $C_2$  and  $C_3$  (the former eczema) and one in group  $C_3$  (severe eczema). These children have been excluded from the calculations for nasal discharge. Corrections for the specific infections have also been made as in Investigation I.

Table 15 shows the results of the calculations of the net morbidity. As weights in the calculation of the joined means for groups  $E_{1-4}$  and  $C_{1-4}$  were used the average numbers of unreduced i-days per month for the E groups (the standard weights).

A comparison of the net and gross morbidity shows that the corrections involved in the calculation of the former did not cause any great changes. A comparison between the E and C materials

Table 15. Net Infection Indices

## Investigation II

Group	Fever		Nasal discharge	Cough	Diarrhoea	Vomiting	Otitis	Febrile pharyngitis	No. of child-days			
	38° C	39° C							col. 5-8	without reductions	with reductions for	calculations in
	1	2	3	4	5	6	7	8				
E <sub>1</sub>	2.43	0.64	24.57	17.57	0.36	0.21	0.07	1.14	1,400	1,400	1,400	1,400
E <sub>2</sub>	3.97	2.20	30.78	21.43	1.04	0.67	0.18	1.22	1,638	1,638	1,423	1,638
E <sub>3</sub>	0.88	0.33	20.59	9.91	1.10	0.44	0	0.50	1,817	1,817	1,598	1,817
E <sub>4</sub>	0.70	0.35	21.04	13.16	0	0.43	0.13	0.26	2,300	2,298	2,300	2,211
E <sub>1-4</sub>	1.83	0.83	23.85	15.09	0.59	0.44	0.10	0.71				
C <sub>1</sub>	2.55	1.05	35.86	21.20	1.51	0.65	0	0.85	1,528	1,528	1,528	1,528
C <sub>2</sub>	2.39	1.12	64.65	23.40	1.12	0.37	0.11	1.06	1,881	1,881	1,457	1,782
C <sub>3</sub>	0.93	0.31	52.44	21.75	0.43	0.31	0.27	0.44	2,255	2,253	1,844	1,738
C <sub>4</sub>	0.90	0.27	30.74	7.98	0.09	0	0.27	0.18	2,230	2,222	2,219	2,230
C <sub>1-4</sub>	1.57	0.63	45.01	17.59	0.61	0.29	0.18	0.58				

Calculations based on institution time.

Table 16. Comparison of Net Infection Indices for Experiment and Control Groups

## Investigation II Net Indices for Fever, Nasal Discharge and Otitis

Group no.	Material		Diff. E-C	D. f.	Variance ratio	P
	E	C				
F e v e r						
1	2.43	2.55	— 0.12	1/27	0.03	> 0.2
2	3.97	2.39	+ 1.58	1/27	1.56	> 0.2
3	0.88	0.93	— 0.05	1/48	0.01	> 0.2
4	0.70	0.90	— 0.20	1/43	0.26	> 0.2
1-4	1.83	1.57	+ 0.26	1/149	0.49	> 0.2
N a s a l D i s c h a r g e						
1	24.57	35.86	— 11.29	1/27	5.35	0.05—0.01
2	30.78	64.65	— 33.87	1/24	29.60	< 0.001
3	20.59	52.44	— 31.85	1/43	61.34	< 0.001
4	21.04	30.74	— 9.70	1/43	4.97	0.05—0.01
1-4	23.85	45.01	— 21.16	1/142	56.07	< 0.001
O t i t i s						
1-4	0.10	0.18	— 0.08	1/149	1.83	0.2—0.05

E = experiment groups

C = control groups

Table 17. The Material in the Various Groups per Month

Investigation II	Group	<i>No. of children</i>							
		Nov.	Dec.	Jan.	Feb.	Mar.	Apr.	May	June
E <sub>1</sub>	7 194	6 157	5 144	7 147	8 149	11 256	9 252	10 101	
	7 167	7 166	9 230	10 240	9 234	9 237	10 262	9 102	
E <sub>2</sub>	9 184	9 234	9 180	9 223	8 208	14 257	15 356	14 175	
	7 68	8 228	13 339	15 346	14 346	14 398	15 424	11 151	
C <sub>1</sub>	6 153	6 186	7 200	6 174	7 215	9 244	9 241	8 115	
	6 147	7 217	10 245	10 290	11 331	12 283	8 248	8 120	
C <sub>2</sub>	12 208	12 289	9 271	10 279	11 331	14 359	15 346	13 172	
	12 131	13 367	16 355	14 327	13 382	11 264	13 279	10 125	

shows that nasal discharge occurs to a decidedly larger extent in the latter, while in other respects the indices do not show any consistent tendency. The result of the analyses of variance for fever, nasal discharge and otitis is given in table 16.

It is clear that the small differences with regard to fever are not statistically probable. The difference between the indices for nasal discharge for the whole E and C materials is statistically significant, as it is also for groups E<sub>2</sub> and C<sub>2</sub> and groups E<sub>3</sub> and C<sub>3</sub>. For both the other groups the difference is probable.

For otitis the difference between E<sub>1-4</sub> and C<sub>1-4</sub> does not reach statistical probability.

The values obtained thus show that nasal discharge occurred to a much lesser extent among children not admitted to the day nursery when they displayed signs of infection, than among those

### Experiment and control groups

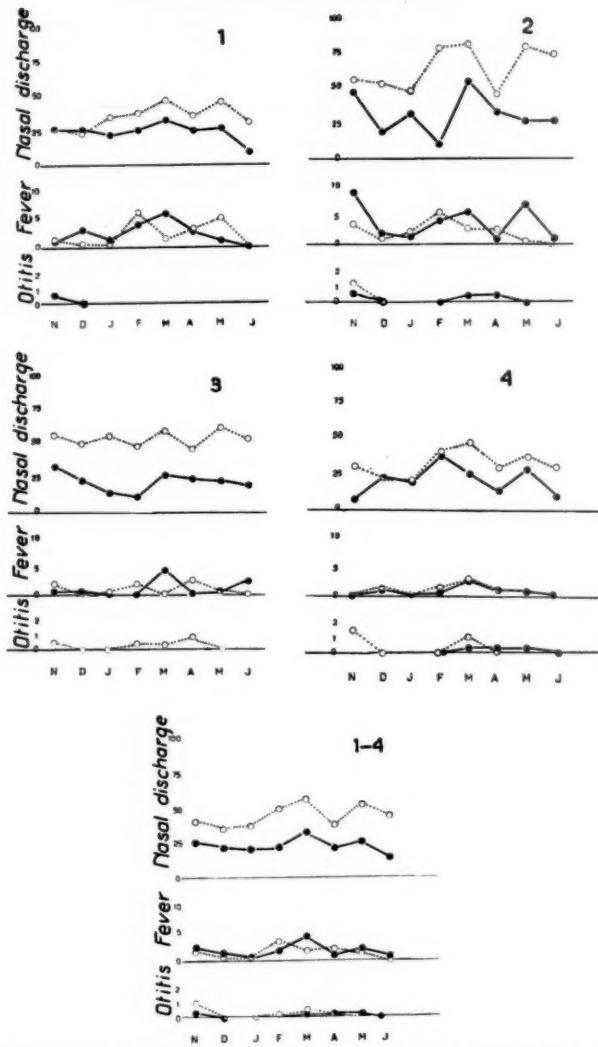
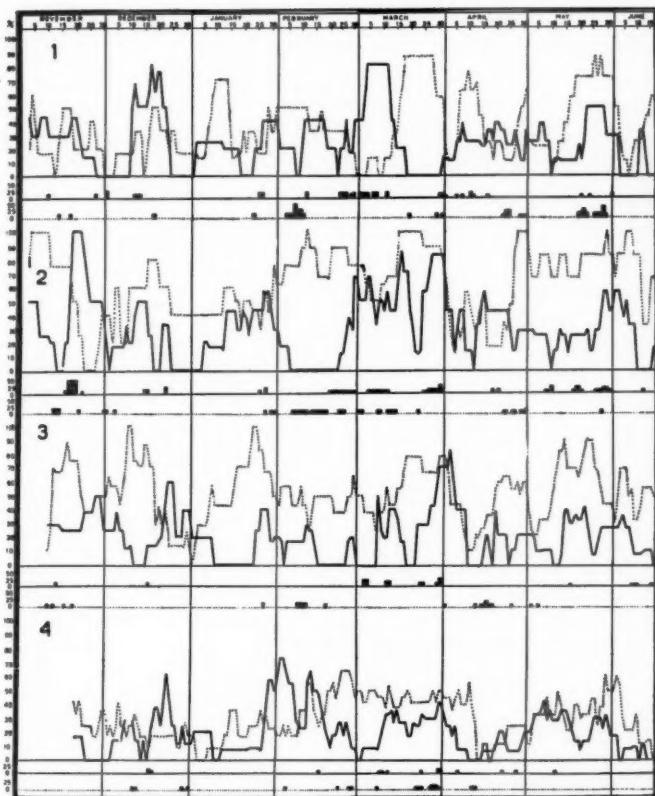


Fig. 6. Graphical representation of net infection indices obtained for nasal discharge, fever and otitis during various months. —●— denotes experiment groups. ○—○—○ denotes control groups.



*Fig. 7. Graphical representation of the daily variations in the net morbidity for the various groups.*

Solid lines denote nasal discharge in experiment groups.

Dotted • • • • • control •

Blocks on solid lines denote fever in experiment groups.

• • dotted • • • control •

admitted in accordance with the usual rules. The differences with respect to other signs of respiratory infections are too small and varying to justify any drawing of conclusions.

### *Variations in the morbidity*

The variations in the morbidity during the investigation time have been recorded in the same way as in Investigation I. The material in each of the one month periods is shown in table 17, and the monthly infection indices are illustrated in fig. 6.

It seems that no definite seasonal variations can be demonstrated for this investigation either. Admittedly, most of the curves suggest that the maximum incidence of sickness occurred in March, with lower values both earlier and later, but this tendency is not uniform.

The development of the sickness incidence from day to day is shown in fig. 7. The curves are, of course, a little too peaked owing to the small size of the material, but seem nevertheless to indicate certain differences between the different groups. Thus, it appears that in group C<sub>2</sub> and to a certain extent in group C<sub>3</sub> also, there seemed to be more extensive and protracted infection waves than in the other groups, a situation which is quite compatible with the observations on similar aspects made in Investigation I (page 62).

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Although it is really outside the scope of this work, it seemed of interest here briefly to illustrate the consequences of the experimental measures upon the E material, in so far as they affect the children's absence frequency. These calculations were based on absence due to net morbidity during the institution time. The possible attendance days here have been counted as the number

Table 18. Absence due to Respiratory Infections  
Investigation II

Group	Non-attendance days (1)	Possible attendance days (2)	Absence rate (1)/(2) × 100	Group	Non-attendance days (1)	Possible attendance days (2)	Absence rate (1)/(2) × 100
E <sub>1</sub>	345	1,049	32.9	C <sub>1</sub>	213	1,142	18.7
E <sub>2</sub>	501	1,245	40.2	C <sub>2</sub>	268	1,337	20.0
E <sub>3</sub>	363	1,351	26.9	C <sub>3</sub>	236	1,431	16.5
E <sub>4</sub>	380	1,612	23.6	C <sub>4</sub>	240	1,489	16.1
E <sub>1-4</sub>			30.1	C <sub>1-4</sub>			17.6

of actual attendance days plus the number of non-attendance days due to respiratory infections. The result is shown in table 18, where the joined means given for the whole materials have been calculated by weighing with the standard weights of the groups (pages 53 and 71).

It is, accordingly, clear that the reduction in morbidity which accompanied the measures taken with the experimental material was achieved at the cost of a considerable increase in absences due to respiratory infections. It may be mentioned that, in order to make a comparison, the net absence-rate of the day nursery material in Investigation I was calculated and found be to 15.6.

## CHAPTER V

### *Morbidity in the two sexes*

The differences between the sexes, with regard to their susceptibility to respiratory infections, has been mentioned in many publications. Some of these papers deal with children and a few of them may be noted here.

In the previously mentioned work of Collins and Gover (1933) the authors found the morbidity for boys aged 0—4 years to be 10 per cent higher than for girls, and for boys aged 5—9 years 3 per cent higher. In an investigation lasting two years and covering nearly 4,000 children Sydenstricker (1927) found differences in the same direction and of about the same magnitude; van Volkenburgh and Frost (1933) had similar experiences in an investigation mentioned further back in this thesis.

A tendency towards a higher morbidity among boys was also established in the two investigations mentioned earlier, on respiratory infection among day nursery children (the Day Nurseries Committee of the Medical Women's Federation 1946, McLaughlin 1947); the difference here was not consistent, however.

Other investigators, e. g. Gyllenswärd (1936), have not been able to show any difference between the sexes in this respect.

The morbidity among the groups of children involved in the present work was, as has been pointed out earlier, originally calculated for boys and girls separately. The differences found between the sexes in the various groups were too variable in tendency and size to form a basis for any conclusions. The following calculations were therefore made on the mean net indices for day nursery, nursery school and home materials in Investigation I, and for the experiment and control materials in Investigation II. The results of these calculations for fever, nasal discharge and otitis are shown in table 19, which also includes mean indices for all the day nursery children ( $D + E + C$ ), all institution children ( $D + N + E + C$ ) and all the children included in the investigations ( $D + N + H_D + H_N + E + C$ ). These indices are weighed means.

Table 19. Comparison of Net Infection Indices for Boys and Girls

Net Indices for Fever, Nasal Discharge and Otitis, and Number of Children

Investigations I &amp; II

 $D = D_{1-4}$ ,  $N = N_{1-4}$  etc.

Groups	Boys		Girls		Difference Boys-Girls	D. f.	Variance ratio	P
	Index	No.	Index	No.				
F e v e r								
$D$ .....	2.84	58	2.16	50	+ .68	1/106	1.65	>0.2
$N$ .....	1.78	46	1.51	60	+ .27	1/104	0.41	>0.2
$H_D$ .....	1.37	44	1.80	40	- .43	1/82	1.03	>0.2
$H_N$ .....	1.60	27	1.44	23	+ .16	1/48	0.13	>0.2
$E$ .....	1.99	43	1.76	39	+ .23	1/80	0.15	>0.2
$C$ .....	1.74	38	1.44	31	+ .30	1/57	0.47	>0.2
$D+E+C$ .....	2.26	139	1.82	120	+ .44	1/257	2.02	0.2—0.05
$D+N+E+C$ .....	2.13	185	1.74	180	+ .39	1/388	2.47	0.2—0.05
$D+N+H_D+H_N+E+C$ ...	1.84	256	1.70	243	+ .14	1/497	0.48	>0.2
N a s a l D i s c h a r g e								
$D$ .....	53.04	55	45.03	49	+ 8.01	1/102	3.51	0.2—0.05
$N$ .....	41.05	45	32.45	59	+ 8.60	1/102	4.26	0.05—0.01
$H_D$ .....	19.95	42	20.19	40	- .24	1/80	0.01	>0.2
$H_N$ .....	14.67	27	24.47	23	- 9.80	1/48	6.42	0.05—0.01
$E$ .....	24.86	42	23.22	38	+ 1.64	1/78	0.31	>0.2
$C$ .....	43.29	35	51.67	29	- 8.38	1/63	2.61	0.2—0.05
$D+E+C$ .....	42.72	132	41.85	116	+ 0.87	1/246	0.10	>0.2
$D+N+E+C$ .....	42.29	177	39.40	175	+ 2.89	1/350	1.45	>0.2
$D+N+H_D+H_N+E+C$ ...	31.47	246	31.65	238	- 0.18	1/482	0.01	>0.2
O t i t i s								
$D+E+C$ .....	0.19	139	0.20	120	- 0.01	1/257	0.08	>0.2
$D+N+E+C$ .....	0.16	185	0.17	180	- 0.01	1/388	0.03	>0.2
$D+N+H_D+H_N+E+C$ ...	0.12	256	0.13	243	- 0.01	1/497	0.13	>0.2

The weighing was based on the number of i-days for the boys in the different groups.

The differences found between boys and girls suggest, as do the majority of the works cited, the possibility of a somewhat higher morbidity among boys than among girls.

The differences were in general relatively small, did not entirely tend in the same direction and, statistically speaking, were not significant. It was therefore considered possible to ignore them, and in the present work the morbidity is calculated irrespective of possible sex differences.

## CHAPTER VI

### *Morbidity in different age and socio-economic groups*

On one or two occasions previously it has been briefly pointed out that signs of respiratory infections indicated a higher morbidity in some groups than in others, the age factor apparently being of particular importance. This has led to the following investigations into the possible relationship between age and morbidity.

The incidence of respiratory infections at different ages in childhood and adolescence has attracted the attention of many investigators. A considerably higher morbidity in the ages 0—4 years and 5—9 years than in older groups was established by Townsend & Sydenstricker (1927), and Collins & Gover (1933), in the course of investigations covering extensive material. van Volkenburgh and Frost (1933) found that, to a large extent, the attack rate sank with increasing age, but that for the 0—1 year group the morbidity was lower than for the next age groups. In his earlier-cited work on institution children, Gyllenswärd (1936) found a decline in morbidity with a rise in age.

The significance of age was studied by Allen-Williams (1945) with special reference to day nursery children. She found a higher morbidity with respect to infections in general, in the 0—2 and 2—4 year age groups than in the ages 4—5 years. The Day Nurseries Committee of the Medical Women's Federation (1946) found a greater difference in the incidence of respiratory infections in day nursery children and home children of 2—3 years of age than in other age groups. The values for nasopharyngeal infections which McLaughlin (1947) obtained in her investigation of day nursery children indicate a higher morbidity in the 1—3 year age group than in older and younger ages. Finally, mention may be made of Frisell's (1948) investigation. He demonstrated the occurrence of higher sedimentation rates in day nursery children under three years of age than in those over this age.

The situation with regard to age in the groups in the present work has already been dealt with to some extent earlier (tables

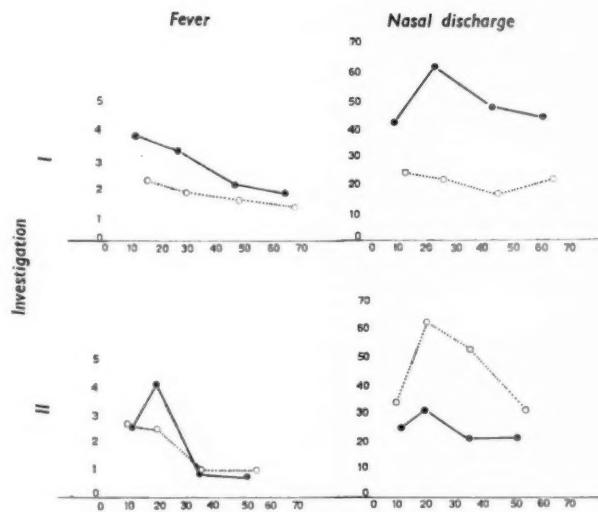


Fig. 8. Graphical representation of net indices for fever and nasal discharge in various age groups. Vertical figures refer to infection indices; horizontal figures to age in months. —●— denotes day nursery groups in Inv. I and experiment groups in Inv. II. ○—○○○ denotes home groups in Inv. I and control groups in Inv. II.

1 and 11). In order to obtain a more exact basis for comparing the morbidity the mean age for the different groups was calculated on the basis of the children included in the calculations with respect to the institution time. The ages of these children midway<sup>1</sup> through the investigations were calculated. The means obtained (like the morbidity indices of the groups) are weighed means where the number of net i-days for each child are used as weights. (For the home children the number of net observation days are used.) The mean values thus obtained are shown in table 20.

The net indices found for fever and nasal discharge in the different age groups in the day nursery material (D) and the home material ( $H_D$ ) in Investigation I, and in the two sections of nursery material, E and C, in Investigation II are shown in fig. 8.

<sup>1</sup> For practical reasons, the midway point was fixed at Feb. 1st, 1947, for Investigation I and March 1st, 1948, for Investigation II.

**Table 20. Mean Age in Various Groups (in months)**  
**Investigations I & II**

Investigation I						Investigation II					
Group	M	$\epsilon$ (M)	Group	M	$\epsilon$ (M)	Group	M	$\epsilon$ (M)	Group	M	$\epsilon$ (M)
D <sub>1</sub>	11.5	$\pm 1.0$	H <sub>D1</sub>	15.5	$\pm 0.7$	E <sub>1</sub>	10.9	$\pm 1.0$	C <sub>1</sub>	9.6	$\pm 0.6$
D <sub>2</sub>	26.2	$\pm 1.4$	H <sub>D2</sub>	29.2	$\pm 1.0$	E <sub>2</sub>	19.4	$\pm 0.8$	C <sub>2</sub>	20.1	$\pm 1.0$
D <sub>3</sub>	46.4	$\pm 1.0$	H <sub>D3</sub>	48.0	$\pm 1.5$	E <sub>3</sub>	35.2	$\pm 1.1$	C <sub>3</sub>	35.4	$\pm 1.2$
D <sub>4</sub>	64.2	$\pm 2.2$	H <sub>D4</sub>	67.4	$\pm 2.3$	E <sub>4</sub>	52.0	$\pm 1.6$	C <sub>4</sub>	54.8	$\pm 1.9$

Tests for homogeneity within each of the four different materials gave the result shown in table 21.

First, as far as the three day nursery materials are concerned, a probable or very probable heterogeneity was found with respect to the occurrence of *fever*. This is obviously due to the fact that fever is a commoner occurrence among younger than among older children, a finding which seems to accord with general experience (e. g. see van Volkenburgh & Frost, Gyllenswärd). In the present materials a boundary line can be traced, which in the D material seems to be located somewhere between 2 and 4 years of age and in the E and C materials somewhere between 2 and 3 years of age. A comparison between the two younger groups (mean age under 2½ years) and the older groups in the respective materials, gives a very probable difference for the D groups (d. f. 1/104, variance ratio 8.63, 0.001 < P < 0.01) and statistically significant differences for the E and C materials (d. f. 1/78, variance

**Table 21. Tests for Homogeneity of Various Age-Groups with Relation to Fever and Nasal Discharge**  
**Investigations I & II**

Investigation	Groups	F e v e r			Nasal Discharge		
		D.f.	Variance Ratio	P	D.f.	Variance Ratio	P
I	D <sub>1</sub> —D <sub>4</sub>	3/104	3.09	0.01—0.05	3/100	3.87	0.01—0.05
	H <sub>D1</sub> —H <sub>D4</sub>	3/80	0.69	> 0.2	3/78	0.93	> 0.2
II	E <sub>1</sub> —E <sub>4</sub>	3/78	8.54	< 0.001	3/76	2.63	0.05—0.2
	C <sub>1</sub> —C <sub>4</sub>	3/65	5.74	0.001—0.01	3/60	13.38	< 0.001

ratio 21.75,  $P < 0.001$  and d. f. 1/65, variance ratio 17.13,  $P < 0.001$ , respectively).<sup>1</sup>

As regards the occurrence of *nasal discharge*, the day nursery materials D and C show a heterogeneity which can be denoted as probable, and significant, respectively. This is obviously connected with the higher indices in the groups with an average age of about 2 years than in the younger and older groups. A similar difference, although of a lesser degree, can also be discerned in the E material. It also seems logical to draw a parallel between these observations and the result of the afore-mentioned British investigations into respiratory infections among day nursery children. A comparison of group no. 2 with the other groups in the same material suggests a very probable difference in the D material (d. f. 1/100, variance ratio 11.05,  $0.001 < P < 0.01$ ) and a significant difference in the C groups (d. f. 1/60, variance ratio 19.57,  $P < 0.001$ ) while in the E groups it can be denoted as probable (d. f. 1/76, variance ratio 6.73,  $0.01 < P < 0.05$ ).

On the other hand, the home material ( $H_D$ ), in comparison with the day nursery materials, displays very small differences between the different age groups. There seems, it is true, to be a tendency towards a lower incidence of fever with increasing age, a circumstance which, taken in the light of what has previously been stated concerning fever among day nursery children, might be attributed some significance. The smallness of the differences is, however, demonstrated by the result of the homogeneity analysis. The result is the same when the differences between the indices for nasal discharge are examined. These values do not otherwise seem to show any tendencies directly attributable to the age factor.

As mentioned earlier, these findings concerning the differences between various age groups in the home material were considered to justify the ignoring of the disparity in the mean ages of institution and home groups in Investigation I.

It has been pointed out further back that besides certain differences in age between day nursery and home groups, there are also certain differences between them with respect to the socio-economic circumstances; the home groups tended to have a some-

<sup>1</sup> The relatively large difference in the E material is, however, connected with the presence in group E<sub>2</sub> of some children with an exceptionally high fever incidence (cf. p. 91).

**Table 22. Incidence of Fever and Nasal Discharge at Two Different Socio-Economic Levels**

**Investigation I**

Groups	Mean age in months	Survey made on Oct. 15th, 1946			Fever index	Nasal discharge index
		No. of rooms	Socio- economic group	Income Sw. Cr.		
H <sub>D3-4</sub>	56.9	1.2	2.2	5,469	1.37	18.27
H <sub>N1-4</sub>	54.5	1.8	1.8	8,780	1.60	20.90

what higher socio-economic standard. To begin with, it seemed rather improbable that these small differences would be of any particular importance as far as the morbidity was concerned. This view receives support from Sydenstricker's (1929) investigation into the economic status and the incidence of respiratory illnesses in a material in which, judging by the living conditions, the differences in question were considerably greater than in the present investigation. He found that the incidence values for the "well-to-do and comfortable" and for the "poor and very poor" were very much on the same level.

The importance of the social and economic factors in the present material can, to a certain extent, be studied by comparing different home groups. Children in the home groups ( $H_N$ ) corresponding to the nursery school lived in better circumstances than children in the home material ( $H_D$ ) corresponding to the day nursery. A comparison of materials more or less uniform as regards age, based on this principle yields the result given in table 22. The values are weighed means, the number of o-days of the  $H_D$  groups having been used as weights.

The differences found in the indices for fever and nasal discharge are, as is seen, not very large, and, as is clear from analyses of variance, might be due to chance (for fever, d. f. 1/85, variance ratio 0.55,  $P > 0.2$ , for nasal discharge, d. f. 1/83, variance ratio 0.67,  $P > 0.2$ ).

This suggests that the relatively small differences in social and economic standards between the day nursery and corresponding home groups are not of great significance in calculations of the morbidity.

## CHAPTER VII

### *Resistance to respiratory infections*

I have already shown that among the day nursery children the younger age groups suffered considerably more from respiratory infections than the older groups, an observation which agrees with the findings of some earlier investigators in the same field. This illustrates the well known increase in resistance which accompanies increasing age in childhood. A question of great importance now is whether an increase in resistance among the day nursery children also occurs through other causes than an increase in age—more especially as a consequence of the frequent infections. This problem is obviously of much practical significance, but I have not been able to find any mention of the question in earlier investigations of day nursery material. It has, on the other hand, been the subject of inquiry in investigations on other material, as has been mentioned on pages 24—26. As stated previously, however, the publications I have been able to study are not unanimous with regard to the existence of such an increase in resistance.

An attempt to illuminate this question from a study of the day nursery materials in Investigations I and II was based on the assumption that any marked increase in resistance that occurred during a stay in the nursery should be reflected in clearly lower morbidity values for the children who had a long stay in the nursery behind them than for the newcomers.

The material at the beginning of both investigations was therefore divided into two sections. One section consisted of "new attenders" whose previous stay in a day or residential nursery ranged from nil to a maximum of  $1\frac{1}{2}$  months, while the other section was composed of "old attenders" and included the rest of the children. Children who came later were assigned to one or other of these groups on the same principles. The net occurrence of fever and nasal discharge during the institution time was then calculated by

**Table 23. Comparison of Net Infection Indices for New and Old Attenders**  
**Net Indices for Fever and Nasal Discharge and Number of Child-Days Used in the Calculations**  
**Investigations I & II**

Group	Average length of stay in months	Fever						Nasal Discharge			
		New attenders		Old attenders		New attenders		Old attenders			
		New attenders	Old attenders	Index	Child- days	Index	Child- days	Index	Child- days	Index	Child- days
Investigation I	D <sub>1</sub>	0	8.1	3.85	1,248	3.68	408	41.35	1,248	48.78	410
	D <sub>2</sub>	0.2	9.9	3.88	902	2.98	2,084	68.74	902	57.13	1,640
	D <sub>3</sub>	0.4	12.5	1.29	310	2.12	3,498	41.29	310	47.40	3,498
	D <sub>4</sub>	0.7	16.9	2.89	900	1.39	3,016	43.68	902	43.72	2,562
	D <sub>1-4</sub>	0.4	12.7	2.76		2.30		48.68		48.77	
Investigation II	E <sub>1</sub>	0.4	2.6	2.31	560	2.50	840	19.32	560	27.74	840
	E <sub>2</sub>	0	2.8	3.72	1,129	4.52	509	32.77	1,129	23.13	294
	E <sub>3</sub>	0	3.0	1.75	514	0.54	1,303	19.84	514	20.94	1,084
	E <sub>4</sub>	0	11.6	1.07	654	0.55	1,644	20.95	654	20.90	1,646
	E <sub>1-4</sub>	0.1	5.6	2.09		1.84		23.15		22.76	
	C <sub>1</sub>	0	2.0	2.36	636	2.69	892	32.55	636	38.23	892
	C <sub>2</sub>	0	3.0	2.66	1,203	2.06	678	65.17	1,005	63.50	452
	C <sub>3</sub>	0.2	8.0	0.60	829	0.98	1,424	59.18	637	48.88	1,207
	C <sub>4</sub>	0	7.4	0.87	803	0.92	1,419	28.82	798	31.81	1,421
	C <sub>1-4</sub>	0.1	5.5	1.50		1.54		45.58		44.65	

the method described earlier. The result is shown in table 23. The total values obtained, D<sub>1-4</sub>, E<sub>1-4</sub> and C<sub>1-4</sub> are weighed means, the groups' standard weights having been used in the calculations. The values for the old and new attenders' average institution time at the beginning of the observation are also calculated as weighed means with the individual children's i-days used as weights.

The differences between new and old attenders at the day nurseries which are shown in the table, are, for some of the individual groups, rather considerable, although pointing in diverse directions. The means calculated for the whole materials differ, however, comparatively little from each other and show no definite tendencies. This relatively good agreement is, as a special calculation suggests, in general applicable to the individual investigation periods.

**Table 24. Comparison of Net Infection Indices for Newcomers and Old Attenders**

**Investigations I & II**

Groups	Indices for			
	Fever		Nasal Discharge	
	Newcomers	Old attenders	Newcomers	Old attenders
D <sub>1-4</sub>	2.18	2.30	44.28	48.77
E <sub>1-4</sub>	1.75	1.84	21.09	22.76
C <sub>1-4</sub>	1.38	1.54	46.19	44.65

The "new attenders" material described above is, however, heterogeneous in that it includes both wholly new children and children who had had a short stay in a nursery. In addition, the children classified as "new attenders" have been counted as such during the whole of their institution time. A further inquiry was undertaken to find out if wholly new children, during their first day nursery period, differed decidedly as regards their morbidity, from the "old attenders". Here the term "newcomers" was applied only to children who had not previously been in a nursery, and the calculations only included the first two months of their day nursery attendance. The two months limit has been chosen with a view to the fact that this would give time for a hypothetical immunity to be established. The result of this is shown in table 24 where mean values for the whole material have been calculated in the same way as described above.

The "newcomers" material is admittedly small (total number of i-days for fever for the D groups = 1,430, for E = 1,704 and for C = 1,394), but it should be possible none the less to attribute some significance to the result since the differences between the indices for the newcomers and old attenders are throughout so trifling and obviously not significant.

The conclusion to be drawn from these comparisons between the morbidity in children who had had little or no previous institution life and that in children who had had a longer nursery or institution stay would seem to be that no considerable differences in the morbidity from respiratory infections between the two groups have been proved. It therefore seems hardly probable that there are any considerable changes in resistance as a consequence of infections occurring during day nursery life.

## CHAPTER VIII

### *Frequency distribution of fever and nasal discharge*

The morbidity analyses performed up to now have dealt mainly with the average morbidity in one or several groups. The calculations whose results are described below attempt to throw light on the background of these averages with regard to the distribution of the morbidity.

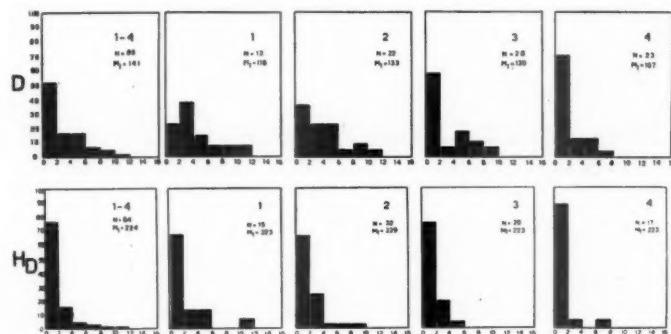
The calculations are based on the individual indices for fever and nasal discharge. With these as a basis the children have been divided into a number of morbidity classes, and the percentage distribution of the children in these classes has been calculated. The calculations are also based on the net morbidity during the institution time (for the home material, during the observation time). In order to make sure that children who had been observed for only a short time would not affect the calculations, only those for whom the period in question was at least 30 days were accepted.

The result is shown in the histograms in figs. 9 and 10. The values for the combined materials  $D_{1-4}$ ,  $N_{1-4}$ , etc., are weighed means, the number of child-days for the various institution groups having been used as weights in these calculations.

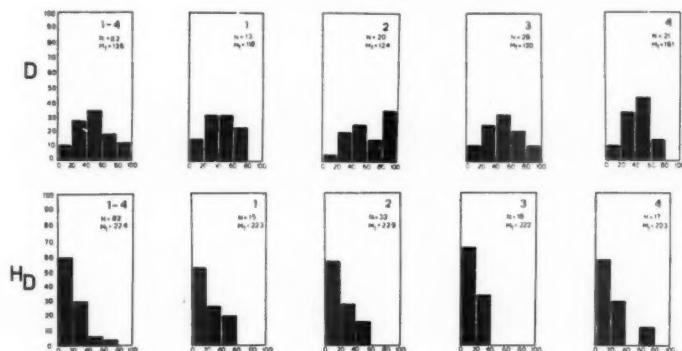
The frequency distributions found are, of course, intimately bound up with the corresponding mean infection indices, but seem, none the less, to give some complementary information. For *Investigation I* the histograms for fever show that about 50 per cent of the day nursery children, about 70 per cent of the nursery school children and about 75 per cent of the home children belong to the lowest fever class (indices 0—1.9). The small index difference between the different age groups in the home material are reflected in the similarity of the corresponding histograms, although the age tendency can be traced here also. Within the day nursery material there is an obvious tendency towards "normalising" of the

### Day nursery and home groups

#### Fever



#### Nasal discharge



### Nursery school and home groups

#### Fever

#### Nasal discharge

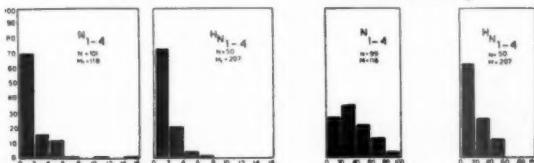
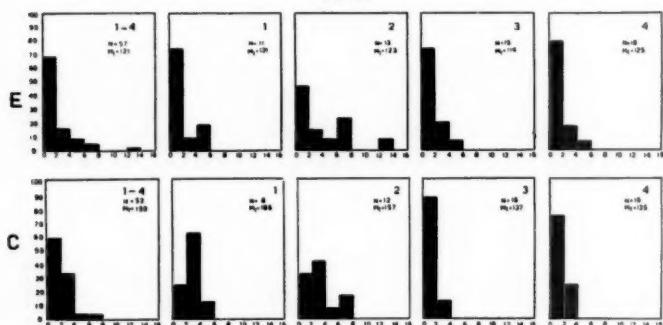


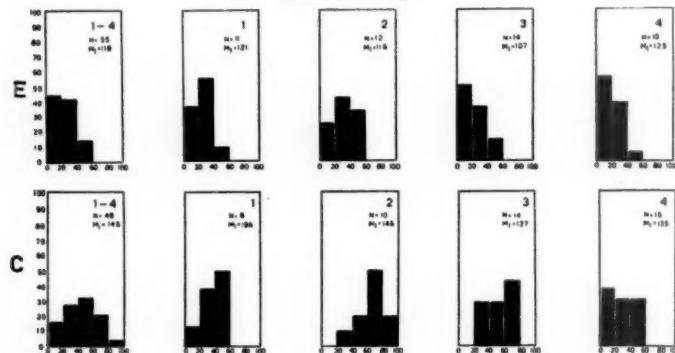
Fig. 9. Frequency distribution of fever and nasal discharge, Investigation I. Vertical figures refer to percentage values; horizontal figures to infection indices. N = no. of children.  $M_i$  = mean no. of i-days for institution children; mean no. of o-days for home children.

### Experiment and control groups

#### Fever



*.Nasal discharge*



**Fig. 10.** Frequency distribution of fever and nasal discharge, Investigation II. Vertical figures refer to percentage values; horizontal figures to infection indices. N = no. of children. M<sub>t</sub> = mean no. of i-days for institution children; mean no. of o-days for home children.

distribution with a rising age where the home material distribution is considered as the norm. Only the two oldest groups show a fairly "normal" distribution.

The histograms for nasal discharge for the day nursery material show that only about 10 per cent of the children had nasal discharge for less than 20 per cent of the institution time. In the home material about 60 per cent belong to this class, in the nursery

school material about 20—30 per cent. Further, it will be noted from the histograms for the individual day nursery groups that children with the highest indices, 80—100, are represented only in groups D<sub>2</sub> (35 per cent) and D<sub>3</sub> (10 per cent). In comparison with this the differences in distribution between various home groups are insignificant.

The material in *Investigation II* was considerably smaller than that in *Investigation I*. The frequency distributions, especially for the individual groups, should therefore be judged with great caution. The histograms for fever for the whole E and C materials seem to show that the distribution in this respect was fairly similar. For nasal discharge, on the other hand, the histograms show quite a different configuration, which, for the C material, is very similar to that depicted above for the D material. The distribution in the E material seems to be displaced to a considerable extent towards that found for home children. As regards the distributions for the individual groups there are some children in group E<sub>2</sub> with specially high fever indices (6—7.9 and 12—13.9 respectively), a fact which naturally influenced the mean value in a high degree. With regard to nasal discharge the distributions for groups E<sub>3</sub> and E<sub>4</sub> show a fairly "normal" picture. Further, it is clear that the highest indices for nasal discharge, 60—100, only occur in the control material, groups C<sub>2</sub> and C<sub>3</sub>.

## CHAPTER IX

### *Discussion*

The chief conclusion that can be drawn from Investigation I is that respiratory infections among children in the day nursery studied were considerably commoner than among children in a comparable home material during the same period. In drawing this conclusion, as well as in other respects in this work, the incidence of these illnesses has been regarded as being represented mainly by the occurrence of some of the leading symptoms. The excess morbidity for the day nursery material as a whole can, it is true, be demonstrated in all respects investigated, but in different degrees. The commonest symptom, nasal discharge, proved to be a very sensitive criterion of infection and occurred in the day nursery material to double, and more than double, the extent that it occurred in the home material. The nursery school material also showed signs of excess morbidity in comparison with the corresponding home material, although to a lesser extent, a fact which is probably connected with the higher age of these children and their shorter institution day.

The question of whether this high morbidity among day nursery children in Investigation I is characteristic of day nursery children in general or is peculiar to a certain day nursery at a certain period, cannot, of course, be given a direct answer. Certain conditions favouring the occurrence of a high morbidity were undoubtedly present at the nursery investigated. It was mentioned earlier that the number of children in the various groups at times exceeded that desirable; also that there were some possibilities of contact between the different groups inside the building, and that children with respiratory infections were admitted on fairly free principles. As regards the period of the investigation, it must be noted that

an influenza epidemic occurred during the period. It was, however, of short duration and, as already mentioned, it seemed improbable that this should have had any decisive influence on the morbidity recorded. It is, on the whole, noticeable that the variations in morbidity during the  $7\frac{1}{2}$  months of the investigation, in the home material also, were not particularly great.

It should however be pointed out that the investigation covered the winter months, and did not include the summer months which, according to general experience, have a lower morbidity.

It is perhaps justifiable to make certain comparisons with the control material in Investigation II, which was undertaken the following year and embraced a more modern nursery with smaller groups carefully separated from each other. Regarding the indices for nasal discharge, the occurrence of this sign of infection among 2-3 year olds is at about the same level as in the Investigation I day nursery material ( $D_2$  61.25 as against  $C_2$  64.65 and  $C_3$  52.44). This applies, however, only to the most susceptible ages. Both older and younger groups show lower indices at the second investigation. In other essential respects, chiefly fever and otitis, the figures confirm the general impression that the day nursery children in Investigation I suffered from more severe types of infection than the children in Investigation II. That this situation is to a certain extent connected with differences in the day nursery conditions seems very probable. Whether other factors, connected with the period covered by the investigation, played any part is impossible to judge.

The value of the comparisons between the institution and home children is wholly dependent on the degree of completeness with which the morbidity among the latter children could be recorded. The opportunity for identically performed observations was not forthcoming. To a certain extent the parents' information had to be accepted direct. Efforts were made, however, to achieve the most effective possible control of the home material and the closest possible contact with the parents.

A number of tests were carried out with a view to obtaining an objective view of certain factors connected with the incidence of infection namely, increase in weight, and the blood's haemoglobin content and sedimentation rate. Chiefly owing to the inconstancy of the day nursery material, however, the results do not allow any

definite conclusions to be drawn and it was therefore decided that they should not be included in this report.

The most important conclusion from Investigation II seems to be that, as far as could be judged by the occurrence of nasal discharge, the rigorous measures for control of infection in the experiment groups resulted in a lower incidence of respiratory infections in these groups than in the control groups. The frequency of other symptoms, especially of fever, was not definitely affected. An explanation of this may be that it was not possible to any great extent to prevent infection occurring and spreading in the groups, but that the length of the infection waves was considerably curtailed.

The question of whether the morbidity in the day nursery groups, particularly the experiment groups, in Investigation II was higher than in a home material cannot be studied directly, for want of a comparable material such as existed in Investigation I. Investigation I home material cannot be used unreservedly, as the two investigations were carried out in different environments and at different times. Possibly, however, one is entitled to point out that the morbidity recorded in the youngest as well as the two oldest E groups does not seem to differ much from that established for the nearest comparable groups in the H<sub>D</sub> material.

The studies on sex differences, as well as those on resistance, with respect to respiratory infections, were mainly carried out for technical reasons in connection with the calculations. The size of the material would hardly justify using the results as support for the theory that there are no true sex differences with respect to the morbidity, or that no changes in resistance occur in consequence of infections in the nursery. It seems unlikely, however, that there are any large sex differences or changes in resistance.

Concerning the morbidity in different ages, comparisons of the infection indices and frequency distributions in different groups ought to yield certain conclusions. It seems clear, for instance, that the morbidity for day nursery material as portrayed by the occurrence of fever is greatest in the younger children below an age of about 2½ years. Nasal discharge as a sign of infection, on the other hand, seems to be commonest among the two-year olds and occurs to a lesser extent both in younger and older age groups. These two findings seem to fit in well with the inference that respiratory infection as a whole is considerably commoner in younger than older

day nursery groups, a conclusion which was also arrived at by certain earlier investigators, in inquiries performed in other ways. The fact that the sign of infection, nasal discharge, is less common among the youngest children of about one year old or less, than among somewhat older children might be considered in the light of the difference between these two age groups with respect to the mode of life and consequently to the conditions for the spread of infection. Thus, the youngest children spend the whole, or most of, the day in their cots, while the somewhat older children's social relationships involve very intimate contact. This circumstance, as well as the fact that the two-year olds usually are assembled in larger groups than the infants, seems to be of significance in the occurrence of the prolonged and refractory waves of infection which are apparently characteristic of this age.

### **Summary**

Chapter I describes first the development of the Swedish day nursery movement and presents a survey of the health problems arising in connection with the care of children in day nurseries. Next follows a review of earlier publications in this field, with particular reference to those dealing with the occurrence of respiratory infections. Finally, the plan of the present communication is described, and it is pointed out that the investigation in question forms part of the research on these problems that has been in progress in Sweden since 1946.

Chapter II describes some of the principles used in the calculation of morbidity. After a brief survey of the literature, the fact is stressed that the group of diseases embracing "respiratory infections" is a very complex one, both from the ætiological and the clinical aspect. It was therefore considered advisable, in the present investigation, to refrain from making any detailed classification of this group of diseases and to regard it, instead, as one unit, characterized by its signs and symptoms. These symptoms, upon which the recording of the morbidity in this study was mainly based, are described and discussed. Further, the concept "morbidity index", on which the calculations are based, is discussed, this concept being taken as implying the number of days with a certain symptom (or the number of attacks of a certain illness) per 100 child-days. The morbidity was calculated both in the form of gross indices embracing the total morbidity, and as net indices, certain reductions having been made in order to obtain a more correct expression for the occurrence of true respiratory infections. The morbidity was also calculated both on the total length of time the children were under observation (the observation time) and also on the time they were regarded as institution children in the narrow sense of the word (the institution time). The analysis of the results is mainly based on the "net indices" during the "institution time".

Chapter III is devoted to Investigation I, which was concerned with the occurrence of respiratory infections among children (a total of 103) at an average type of day nursery where no special precautions against infection had been taken, as well as among children (96) at a nursery school, and among a comparable series of children being reared in their homes (134 children). The investigation embraced the time Oct. 15, 1946 to May 31, 1947. The premises, staff and daily routine of the institution studied are described in some detail. The institution children were observed by means of daily inspection at the institution and, in case of illness, by visits to their homes. The home children were examined periodically, and in addition, frequent visits to the homes were also undertaken. To a large extent, however, the registration of the morbidity among the home children was based on spontaneous reports supplied by the parents. Reliable reports with regard to even slight symptoms were surprisingly easy to obtain.

A detailed account is also given of the characteristics of the different groups, and the comparability between them is discussed. There were four day nursery groups, comprising the age groups  $\frac{1}{2}$ — $1\frac{1}{4}$ ,  $1\frac{1}{4}$ —3, 3— $4\frac{1}{2}$ , and  $4\frac{1}{2}$ —7 years. There were also four nursery school groups, one group being composed of 3—5 year olds and the others of 4—7 year olds.

Calculation of the gross morbidity in the different groups proved that in general the signs of infection registered were much more frequent occurrences among the day nursery children than among the home children. A corresponding difference, though less marked, was observed with respect to the nursery school children. Calculation of the net morbidity, carried out with respect to fever, nasal discharge, cough, diarrhoea, vomiting, otitis and febrile pharyngitis (and tonsillitis) revealed similar results (table 7). The differences were manifest in all these respects for the day nursery material as a whole in comparison with the home material. Statistical calculations revealed a probable difference for fever of  $38^{\circ}\text{C}$ , a significant difference for nasal discharge, and a very probable difference for otitis. With regard to the nursery school children, the differences between institution and home children were significant only with respect to the commonest sign of infection, namely, nasal discharge.

The sickness during different stages of the investigation time showed fairly small variations, a finding which may be described

as surprising, in view of the fact that a severe influenza epidemic involving a high general sick-rate occurred during the course of the investigation. An analysis of the morbidity during each day of the investigation time as reflected mainly by the occurrence of nasal discharge indicated that there were severe protracted waves of infection particularly in the day nursery group including the 2 year olds, while especially among children belonging to the oldest day nursery group, and among the nursery school groups, infection waves were of considerably shorter duration.

Chapter IV deals with Investigation II, the object of which was to endeavour to ascertain to what extent the morbidity among day nursery children could be reduced by strictly refusing admittance to all children with even the slightest signs of infection. Such a measure was adopted with respect to one half of a modern day nursery (called the experiment material) while in the other half, for the sake of comparison, the children continued to be admitted in accordance with the customary principles (the control material). Both series comprised four groups of children ranging in age from 3 months to 6 years, or a total of 145 children. The investigation covered the period November 1947 to June 1948. The institution studied, as well as details with regard to the different groups, are described in the same manner as for Investigation I.

Calculation of the morbidity, as it was reflected in the net indices, revealed that nasal discharge occurred to a significantly lesser extent in the experiment material as a whole than in the control material. In other respects, it was not possible to draw definite conclusions on the basis of the comparisons between the two series (table 15).

No appreciable variations in morbidity [were demonstrated for the different monthly periods. An analysis of the morbidity for each day to some extent seemed to indicate that, in this Investigation also, prolonged waves of infection had been particularly common among the 2 year olds, especially those in the control series.

A brief account is also given of calculations made to ascertain the incidence of absences due to respiratory infections in the two series. While the absence rate for the control group was calculated at 17.6 per cent the rate for the experiment group was 30.1 per cent.

In Chapter V will be found a study of the incidence of respiratory infections in the two sexes, examined by means of analysis of the

occurrence of fever, nasal discharge and otitis in each series separately and then in the combined material. No significant differences between the values obtained for boys and girls were established.

Chapter VI is devoted mainly to examination of possible differences between different age groups with respect to the incidence of respiratory infections. It was found that the sick-rate was definitely higher among the younger day nursery children than among the older children, and that especially among children around the age of 2 years it was at a high level. The findings with regard to children in the home groups, among whom only relatively slight differences were demonstrated between the different age groups, are in striking contrast to this.

Chapter VII examines the question of whether changes in the powers of resistance occur as the result of infections sustained during institution life. This aspect was studied by means of an investigation into the incidence of fever and nasal discharge among new day nursery children as compared with the incidence among children who had been members of a nursery for a longer period. Nothing was observed to indicate that such changes in resistance take place.

In Chapter VIII, the children in the different groups were distributed on certain morbidity classes based on the occurrence of fever and of nasal discharge, respectively. On the whole, the differences in morbidity already demonstrated between day nursery groups of different ages were further illustrated by this study.

Chapter IX presents a general discussion on the results obtained.

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# STILLES

— föregångare inom modern spädbarnsvård —

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En efterlängtad nyhet, det "fulländade" skötbordet, har just kommit ut i marknaden. Det nya skötbordet har den moderna höjden, som tillåter mamman/skötterskan att stå upp-rätt vid skötseln av den lille. Skötbordet har utrustats med flera praktiska detaljer, såsom en hylla att lägga kläder m. m. på, bekvämt placerade fickor för tvål, puder, tvättlappar etc., så att man har allting till hands vid skötseln av den lille.

**A.-B. STILLE-WERNER · STOCKHOLM 4**

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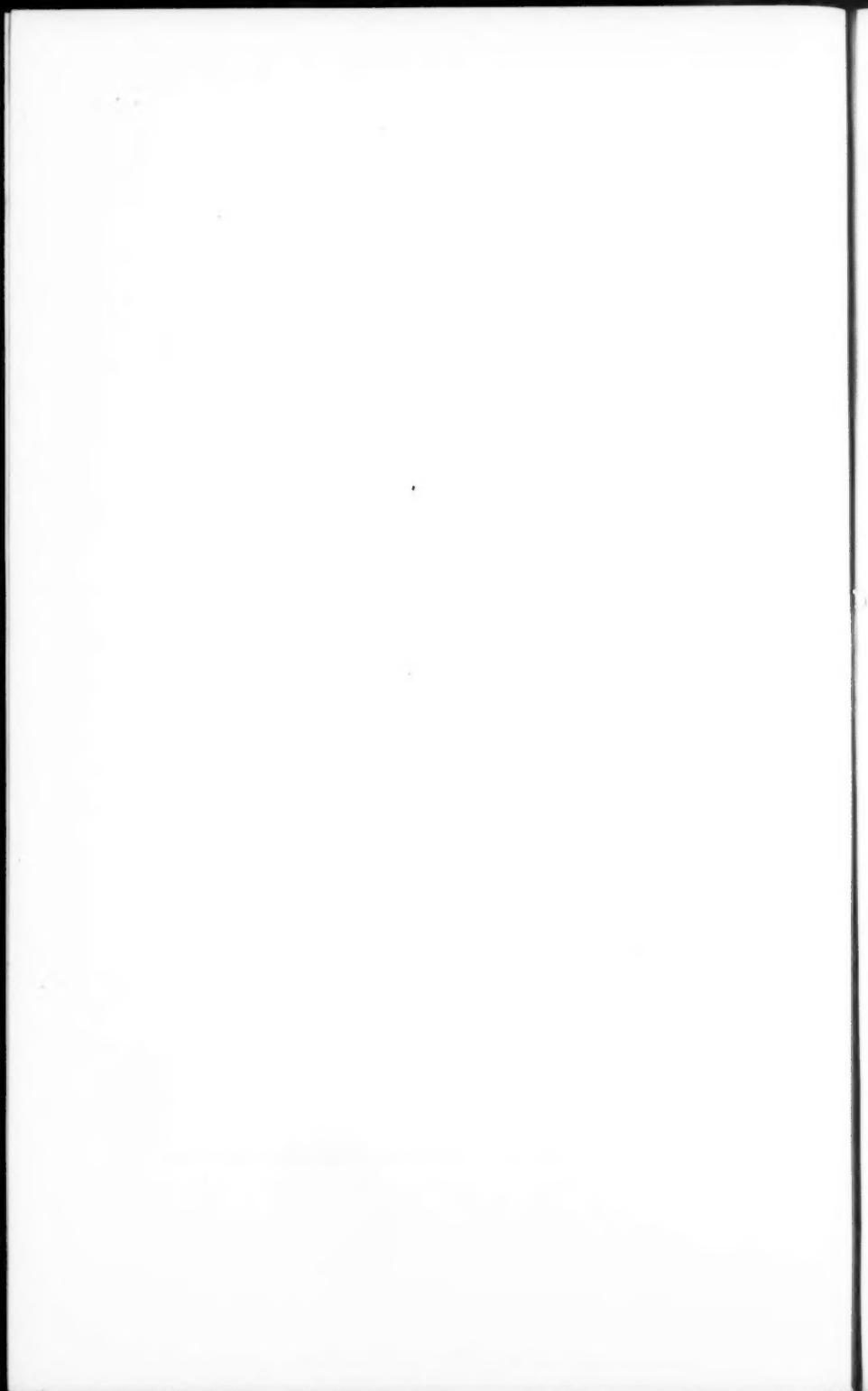
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*Dedicated  
to the  
BRITISH PAEDIATRIC ASSOCIATION  
in remembrance of the visit of  
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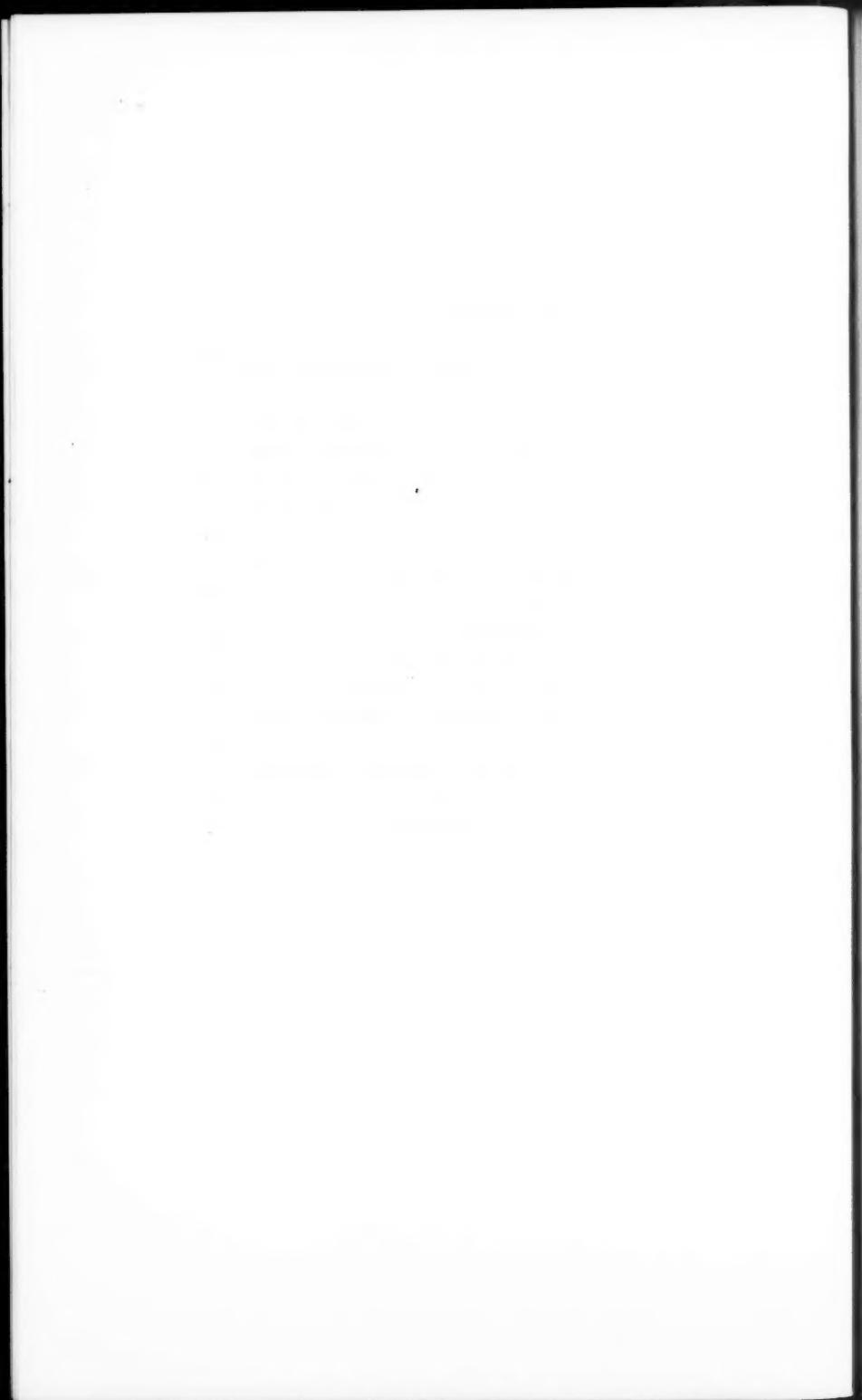
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FROM THE PEDIATRIC CLINIC OF KAROLINSKA INSTITUTET AT KRON-  
PRINSESSAN LOVISA'S CHILDREN'S HOSPITAL, STOCKHOLM. (CHIEF: PRO-  
FESSOR A. LICHTENSTEIN.)

## **Streptomycin in Miliary Tuberculosis and Tuberculous Meningitis**

by

**A. LICHTENSTEIN**

(Lecture Delivered at the Ninth Scandinavian Pediatric Congress,  
Copenhagen, August 1948)

The discovery of streptomycin and demonstration of its effect on acid-fast bacilli has naturally attracted much attention and raised high hopes. All over the world this antibiotic substance is now being tested on various forms of tuberculosis. There is, of course, particular interest in the results in cases of hematogenous tuberculosis, as these forms of the disease are good test objects because of their almost invariably bad prognosis.

At this time, when streptomycin has been employed in various forms of tuberculosis for about two years, it seems to me appropriate to try to form some idea of its efficacy in these cases. We have reports, some of them, covering large series of cases, from both America and Europe. I have found reports on about one thousand cases of meningitis. Speaking generally, the lives of c. 30—40 % have been saved. Apparently, judging from the often incomplete information given, only about one third of these, i. e. c. 10—15 % of the cases treated, can be considered cured or virtually cured, however. The remainder show physical and psychical deficiencies. It should also be noted here that the figures on successfully treated cases are to be regarded as representing a maximum. In view of the frequency of late relapses, the observation period at the time of publication had undoubtedly been too short for a large number of the cases. An observation period of at least one year, possibly even more, is necessary.

In miliary tuberculosis without meningitis, the results are considerably better. Nevertheless it is noteworthy that in not so few cases a secondary meningitis set in during or after the streptogen treatment.

Hitherto sixty-odd cases have been treated in Sweden. Of these, however, only twentyfour have been observed so long that it seems safe to evaluate the results. Only five of these are alive and in satisfactory condition — although all have vestibular injuries. Fourteen are dead and four unsatisfactorily cured or chronically ill (we lack information on one case).

Thus it is evident that streptomycin can save cases of miliary tuberculosis and tuberculous meningitis. On the other hand, it is equally evident that only a small percentage, particularly of the meningitis cases, are restored to complete or almost complete health. The great majority either die or are not completely cured. I should like to emphasize the fact that a number pass into a chronic or sub-chronic state. The streptomycin produces, in fact, a disease picture previously scarcely observed, a sub-chronic tuberculous meningitis with cachexia, paralyses, convulsions and often partial or total block with hydrocephalus and marked psychical deterioration.

In judging the value of streptomycin in tuberculosis one must bear in mind that the effect of this substance on the tuberculosis bacillus is mainly a bacteriostatic one and only to a small extent a bactericidal one, at any rate in the concentrations which occur in the fluids or organs of the body (with the possible exception of the kidneys). In one of my cases the presence of tubercle bacilli in the liquor and fresh miliary tubercles in the meninges could be established in connection with an operation for ventile-hydrocephalus undertaken eleven months after the onset of the disease, when the patient had received c. three hundred grams of streptomycin.

Certain experimental investigations indicate, however, that the effect of streptomycin on living subjects is not merely a function of the concentration. There may also be some kind of indirect effect. The mechanism by which the substance works is not yet understood.

A number of other factors concerning streptomycin also remain obscure. These include its resorption, distribution and excretion. The concentration in the cerebrospinal fluid is of particular interest. Apparently it varies widely; in my cases it varied between one and eight units per cc. during periods of intramuscular injection only, although it was usually only one to two or below — i. e., a lower concentration than is ordinarily required for retarding the growth *in vitro*. Yet it should be pointed out that a number of meningitis cases have been saved by intramuscular treatment only.

Our knowledge is also deficient concerning both the best manner of administration and the optimal dosage; this applies equally to the amount of the individual dose, the number of doses per day, and the length of the treatment period.

Where dosage is concerned, two considerations must be kept in mind; the toxic effect of the streptomycin, particularly on the vestibular nuclei, and the risk of inducing resistance. It is a question of Scylla or Charybdis. The toxicity forces us to keep the dosage down, but small doses probably increase the danger of inducing resistance. The extent to which the tuberculosis bacillus in the living body becomes resistant is still not known. Resistance comes into existence easily *in vitro* however.

At present my dosage is one hundred mg four to six times daily intramuscularly and twentyfive to fifty mg intrathecally, at first once a day but later every other or every third day over three-week periods for at least four to five months. I attempt, however, to reduce both the amount of the individual doses and the number of injections per day. If it should appear that maintenance of a constant streptomycin concentration in the blood and body fluids is not necessary, it might be possible to reduce the doses considerably and thereby also the danger of harmful secondary effects.

Treatment of tuberculous meningitis must, finally, always present the difficulty that because of poor vascularization of the brain substance, any intracerebral foci are very difficult for therapeutic agents to reach. It is then an open question whether treatment of the primary infection, by means of which

one might be able to prevent meningitis, would not be preferable. Undoubtedly this would be right if we had access to an effective and atoxic substance. Streptomycin is so toxic, however, that it very often causes irrevocable vestibular injuries. These may follow after only a few grams — in one of my cases after only six and a half grams — although they are much more common after larger doses. Injuries to the cochlear nuclei with resultant partial deafness also occur, if more rarely. The toxicity of streptomycin is such that I for my part do not consider it suitable for treatment of ordinary primary tuberculosis, benign as it usually is.

To summarize, streptomycin has marked the beginning of a new era in the history of the treatment of tuberculosis. For the first time we have a substance at hand with which we may be able to save a number of cases of formerly almost hopeless types of disease. But the effect is still often too weak and uncertain. In many respects streptomycin treatment of tuberculosis is still in an experimental stage. Last but not least, the substance is not atoxic. Further studies must reveal whether perhaps we have more to gain by combining streptomycin with other media, for example certain sulfa preparations. Some experiences would seem to indicate this. Certainly it is desirable that we obtain a new atoxic substance with not only bacteriostatic but also bactericidal effect.

#### **Summary**

Hematogenous tuberculosis can be healed by streptomycin. The author stresses the fact that up to now only about 10—15 % of the cases have been cured, that a number of factors concerning streptomycin still are obscure, that streptomycin is toxic and that its effect is mainly bacteriostatic.

#### **Résumé**

La tuberculose hématogène peut être guérie par la streptomycine. L'auteur insiste sur le fait que jusqu'ici seulement 10—15 % des cas ont été guéris, que nombreux de facteurs concernant la streptomycine sont encore obscurs, que la streptomycine est toxique et que son effet est surtout bactériostatique.

**Zusammenfassung**

Haematogene Tuberkulose kann durch Streptomycin geheilt werden. Der Autor betont die Tatsache, dass bis jetzt ungefähr 10—15 % der Fälle geheilt wurden, dass in Bezug auf das Streptomycin eine Reihe Faktoren noch dunkel sind, dass Streptomycin toxisch und sein Effekt hauptsächlich bakteriostatisch ist.

**Sumario**

La tuberculosis hematógena se puede curar mediante estreptomicina. El autor hace recalcar que entre el diez y el quince por ciento de los casos se han curado, que no se conocen bien todavía un gran número de factores relacionados con la estreptomicina, que la estreptomicina es tóxica y que sus efectos son principalmente bacteriostáticos.

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FROM THE PEDIATRIC CLINIC OF KAROLINSKA INSTITUTET (CHIEF: PROFESSOR A. LICHTENSTEIN) AND THE DEPARTMENT OF SURGERY (CHIEF: PH. SANDBLOM, M. D.) AT KRONPRINSESSAN LOVISA'S CHILDREN'S HOSPITAL, STOCKHOLM.

## A Contribution to the Knowledge of Banti's Syndrome

With Special Emphasis on Differential Diagnosis and Treatment

by

L. E. CARLGREN, A. LICHTENSTEIN, and PH. SANDBLOM

Splenomegaly with or without anemia is a common symptom in infants as well as older children. In some cases, such as infectious disease of different kinds, including typhoid fever, sepsis, tuberculosis, syphilis, and malaria, the etiology is obvious. In others hypertrophy of the spleen is but one of a number of symptoms in some systemic disease in the hematopoietic apparatus, such as leukemia, lipoidosis, lymphogranulomatosis, or hemolytic ieterus. In addition to these, however, one also encounters a large group of splenomegalies of uncertain or unknown etiology, without pathogenetic or anatomical conformity but with a number of clinical symptoms in common, including, besides hypertrophy of the spleen, usually anemia, often leukopenia and thrombocytopenia, not infrequently hemorrhages from esophageal varices or a general hemorrhagic tendency, and in many cases signs of liver damage.

### *Terminology*

These conditions have long been grouped together under the general heading *splenic anemia*. The term is still widely used in the Anglo-Saxon literature, while *Morbus Banti* has become more popular in the Romance and Germanic literature. Even in Anglo-Saxon authors one occasionally finds the expression *Banti's disease* or *Banti's syndrome* as a synonym for splenic anemia, however.

In the course of time the conception of a specific Banti's disease (BANTI 1883 and afterwards), with the classical three stages, has been subjected to a good deal of criticism, and at present most authors doubt its existence. A similar clinical picture may arise in many different pathological conditions with a common center in the portal circulation. PATRAZZI (1942) thoroughly covered all the abundant literature in the field but could not find any better name for the condition in question than *Banti's syndrome*, by which he meant all the disease complexes of different or unknown etiology, with or without liver damage and with or without hemorrhages of the digestive tract, the symptomatology of which was based on considerable, usually progressive hypertrophy of the spleen with the character of fibroadenia or congestion.

#### *Pathogenesis*

On the subject of pathogenesis opinions are still widely divergent. According to BANTI himself, hypertrophy of the spleen was primary, caused by an unknown infectious toxic agent, while hepatic cirrhosis constituted a development secondary to changes in the spleen.

According to the opposite school of thought, represented chiefly by WHIPPLE and ASSOCIATES of the Spleen Clinic at the Presbyterian Hospital in New York, enlargement of the spleen is secondary to changes in the liver or portal bed. They hold that the essential element in Banti's syndrome is a hypertension in the portal or splenic vein resulting from a block in the portal circulation which may be either intrahepatic (cirrhosis) or extrahepatic (usually thrombosis of the portal or splenic vein). Hypertrophy of the spleen arises in a purely mechanical way, through stasis. This opinion is based on direct measurements of pressure in a large number of cases in connection with splenectomy (THOMPSON and ASSOCIATES 1937) and is further supported by experiments with animals (ROUSSELOT and THOMPSON 1939).

When the pressure in the portal circulation becomes higher than in the caval system, the result is a widening of the anastomoses between the two systems. Such anastomoses are found along the

esophagus and anus and in the abdominal wall. They may expand into sack-shaped formations and are then easily vulnerable. Particularly those in the mucous membranes of the digestive tract may give rise to bleeding, from occult to alarming and dangerous.

For the above-mentioned reasons WHIPPLE and ASSOCIATES prefer the term *congestive splenomegaly* to splenic anemia or Banti's syndrome. This concept is, however, far from covering all the conditions which belong here. In many cases of splenomegalous hepatic cirrhosis there are no signs of an increase in pressure in the portal circulation, as is also the case in the majority of so-called idiopathic enlargements of the spleen.

RAVENNA's opinion<sup>1</sup> (1943) is exactly contrary to that of WHIPPLE and ASSOCIATES. He considers that the enlargement of the spleen cannot be explained as a result of obstruction to the portal circulation. Compression of the portal vein or splenic vein by, for example, a tumor or fibrous adhesion does not lead to enlargement of the spleen; neither does chronic cardiac failure bring about splenomegaly. Attempts to induce splenomegaly experimentally by simple ligation of the splenic vein have also failed. In RAVENNA's opinion the primary change in Banti's syndrome is an *active hyperemia* of the spleen resulting from damage to the splenic capillaries. If simultaneously the portal circulation is obstructed (thrombosis, phlebosclerosis), this is not the cause but a result of the hypertrophy of the spleen.

According to a third explanation, one has to do with a pathological process acting simultaneously in the whole hepato-lieno-portal system, in which now one and now another part of this system may be most affected.

To be sure, in the beginning of this century and even later, *chronic portal and splenic vein thrombosis* was represented as an independent condition, separate from Banti's disease. This condition, however, has so many points of contact with the other cases of Banti's syndrome that it may appropriately be included in this group.

Whatever point of view one adopts with regard to the pathogenesis of these conditions, it seems best to try to classify them

into (I) those in which the liver is affected (splenomegalous hepatic cirrhosis); (II) those in which the damage seems to have affected particularly the portal vein and its tributaries (so-called portal or splenic vein thrombosis); and finally (III) those in which for the most part the spleen alone is the seat of the pathological changes (so-called idiopathic enlargement of the spleen).

#### *Object of This Investigation*

This investigation is not intended as a further contribution to the discussion of the pathogenesis of these conditions, obscure as they still remain in spite of extensive research. It is chiefly because new surgical methods of treatment have opened up that we have felt it worthwhile on the basis of our personal material to throw some light upon the differential diagnosis in conditions resembling Banti's syndrome and to present our therapeutic experiences. In addition, a survey of the modern literature on this subject will be given.

#### *Material*

The material presented here includes those cases of splenomegaly admitted to Kronprinsessan Lovisa's Children's Hospital which showed symptoms mentioned above as criteria of Banti's syndrome, namely, in addition to hypertrophy of the spleen, anemia, leucopenia, thrombocytopenia, gastroesophageal hemorrhages or a general hemorrhagic tendency, and possibly damage to the liver. Only those cases have been included, however, which were sufficiently thoroughly examined, and for this reason most of them date from more recent years.

The material has been divided into two groups, consisting (I) of cases showing clinical symptoms of hepatic disease (icterus, urobilinuria), and (II) of cases in which there were no such symptoms. For the sake of comparison one case of hepatic cirrhosis without splenomegaly was included in the former — the only such case treated at the department during the period in question. In one of the cases belonging to the first group the clinical symptoms of hepatic cirrhosis were not very marked, but upon splenectomy the liver showed pronounced cirrhotic changes. In all

the cases in the second group the liver proved upon operation to have a macroscopically normal appearance. In a number of them, indeed, functional tests revealed that the liver was also affected to some extent, even though the clinical picture showed no signs thereof as it did in the cases in Group I. The symptoms in the cases belonging to this group correspond to those produced by a block in the portal or splenic vein and in a number of them such a block could be proved.

### I. Splenomegalous Hepatic Cirrhoses

The cirrhosis cases include two boys and five girls. Their ages when the symptoms first appeared ranged from five to eleven. The etiology is unknown. According to PFAUNDLER-SCHLOSSMAN acute infections such as scarlet fever and typhoid fever are of etiologic significance in many cases. We have not been able to confirm this with our material. In two of the cases the disease developed in connection with acute hepatitis (5, 7).<sup>1</sup> Tuberculin tests and Wasserman have been negative in all cases.

#### *Symptomatology*

In all cases the disease began insidiously. The most general *early symptoms* were lassitude and lack of appetite. In three cases (3, 4, 5) the child showed a marked tendency to nose-bleeds. Slight or moderate jaundice along with fatigue was the first symptom in two cases (2, 7).

*Hypertrophy of the spleen* is a common and often early symptom in juvenile cirrhosis and may sometimes dominate the clinical picture over a long period, while damage to the liver may be but little in evidence. According to AMBERG splenomegaly occurs in approximately 90 % of hepatic cirrhoses in children. Our cases confirm this observation; the symptom was apparent in all but one (3). In four cases an enlarged spleen could be palpated as early as the first examination. In Case 4 enlargement of the spleen could in the beginning be ascertained only roentgenologically. We have no information as to whether or not

<sup>1</sup> The numbers in brackets refer to the case reports.

the spleen was palpable in the remaining case (7) when treated for the first attack, but considerable splenomegaly was later established. In general the enlargement of the spleen has displayed a noticeable tendency to progress during the later course. In three cases the spleen was examined macro- and microscopically, namely in (4), in which splenectomy was undertaken, and in (2) and in (6), which underwent autopsy. In these cases it weighed, respectively, 500, 400, and 1 200 g. The histological picture was characterized by fibroadenia — i. e. the change which is found in Banti's syndrome.

In two cases (1, 4) the *liver* was distinctly enlarged in the beginning both clinically and roentgenologically. In one of these (1) and in two others (2, 3) which showed a liver of normal size from the beginning, repeated X-ray checkings showed progressive shrivelling. Two of these three patients died two and four years, respectively, after the appearance of their first symptoms, but the third (3) still enjoys obvious good health eight years later despite distinct signs of damage to the liver. In the third of the three cirrhotic patients who died, the size of the liver could not be determined by X-ray but autopsy showed it to be considerably decreased. On this basis one is presumably justified in concluding that a progressive decrease in the liver shadow on the x-ray picture is prognostically an unfavorable but not an absolutely fatal sign. In the two cases which underwent postmortem examination the liver had a typically cirrhotic appearance, and this was also true of the case subjected to splenectomy.

There has been moderate *anemia* of hypochromic or normochromic type with hemoglobin values of 8 g % to 11 g % and 2.5 to 3.5 million red blood corpuscles in only two cases (1, 7). *Leukopenia* of 3 000—5 000 white blood corpuscles has been more common and occurred in four cases (2—5). Differential count has usually revealed slight to moderate relative lymphocytosis. The most constant blood change has been *thrombocytopenia*, which occurred in all cases. For the most part it has been moderate, with values between 50 000 and 150 000; in one case (4) they were as low as 30 000 to 50 000. All the blood changes mentioned here are described in the literature, but it seems as

though thrombocytopenia as a symptom of splenomegalous hepatic cirrhosis has not been sufficiently emphasized. The cases in this series which terminated fatally did not show more serious changes in the blood picture than the others. Thus, judging from this, the degree of blood changes permits of no prognostic conclusions.

*Sternal puncture* was performed in all cases but one (1), usually several times during the course of the disease. The bone marrow showed no characteristic changes. In general the specimen was rich in cells, with hyperplasia particularly of the erythropoietic and the reticuloendothelial elements, while the myelopoiesis remained for the most part unaffected. The megakaryocytes were sometimes numerous and sometimes scarce. The examination seems to have no diagnostic or prognostic value in these cases.

In all cases but one (4) there was slight to moderate *jaundice*, and the *icterus index* according to Meulengracht varied between 1: 15 and 1: 55. In only one case (2) did the value rise just before death to 1: 100. The indirect Hijman van den Bergh reaction was usually more or less markedly positive, while the direct reaction was often negative or only slightly positive. Presumably this indicated that the *icterus* owed its existence at least in part to increased blood destruction and not merely to liver damage. As early as 1920 EPPINGER showed by quantitative determinations of the urobilin excreted with the feces that this does occur in splenomegalous hepatic cirrhoses. The increased blood destruction cannot be explained by decreased osmotic resistance of the red blood corpuscles; this circumstance has been confirmed in this material in that all cases showed *normal* or in some cases *even increased resistance*.

More or less pronounced *urobilinuria* has been a constant finding in these cases even in the earlier stages of the disease. Bilirubinuria, on the other hand, has occurred only in the final stages (2, 6) and is thus an indication of well advanced liver damage.

The appearance of *ascites* in hepatic cirrhosis is regarded as prognostically a poor sign, and our material has confirmed this.

This complication arose in three cases (1, 2, 6), all of which died within a period varying from a few days to approximately a year. In one of these the ascites was probably due in part to stasis in the portal circulation, since in the last stage of the disease the patient showed still other signs of portal hypertension, including gastroesophageal hemorrhages and a widened venous net on the abdomen. At autopsy considerable esophageal varices were also revealed. Since there were no such symptoms in either of the other cases, the ascites in these may have had another origin.

The absence of signs of portal stasis in all our cases of splenomegalous hepatic cirrhosis except the one just mentioned is worthy of note, and the difference in this respect from the next group is marked. It is alleged that in adults hemorrhages from esophageal varices occur in about half of all cases of hepatic cirrhosis (McINDOE 1928). One obtains no clear conception of the frequency of portal hypertension in juvenile hepatic cirrhosis from study of the literature. There may be a difference here between adults and children, but our material is of course too limited to permit any definite assertions on the subject.

*A general hemorrhagic tendency* is a common symptom in hepatic cirrhosis and has occurred in our material in more than half of the cases, particularly in the form of epistaxis and cutaneous hemorrhages. In view of the constant thrombocytopenia in our cases, the explanation of this lies close at hand. Another significant factor is the *prolongation of the prothrombin time*, which is also a common symptom in hepatic cirrhosis. Moderate prolongation occurred in four of our cases (2, 3, 4, 6) with a highest value varying between 45 and 100 seconds according to Fiechter's method (normal value at most 25 sec.). In one case (1) the prothrombin time was not determined. In two cases (2, 3) vitamin K treatment was attempted but without any obvious effect. One of these patients died a few years later as a result of liver insufficiency. In the other case the prothrombin time later returned to normal simultaneously with the patient's clinical improvement. Thus the failure of vitamin K treatment to show any effect need not be a poor sign from the point of view of prognosis.

There was slight prolongation of the bleeding time or clotting time in three cases (2, 3, 4), but this did not occur constantly during the course of the disease.

*Liver function* was studied with the usual tests. The Takata reaction was obtained in all cases and was positive in all but one (4). Of the other tests, the galactose and thymol test, fractionated serum cholesterol and protein determination, and determination of citric acid and phosphatase were carried out to varying degrees. The results did not always coincide. Negative results from one or more tests were not unusual and thus do not exclude liver damage. A glucose tolerance test was carried out in one case (4) and showed a faintly diabetes-like curve as described in hepatic cirrhosis.

Cardiac enlargement and electrocardiographic changes indicating *myocardial damage* were established in two cases, both of which died (2, 6). In one of these (2) distinct clubbed fingers appeared towards the end, a symptom which has been described in connection with hepatic cirrhosis (AMBERG).

It has been alleged that teleangiectasia in the face is an early symptom of latent cirrhosis and this occurred in one of our cases (2).

Prolonged *subfebrile temperature* is sometimes noted in cases of hepatic cirrhosis and was found in one of our cases (5). A symptom which has not been given the attention which is its due, on the other hand, is an *increase in the erythrocyte sedimentation rate*. This occurred in all our cases, with values between 40 mm and 120 mm particularly in the earlier stages of the disease. Later on the sedimentation rate gradually returned to normal in the cases which ended in death (1, 2, 6) as well as in the patients who showed clinical improvement. This increase in the sedimentation rate was presumably caused by an inflammatory process in the liver which gradually receded, later to enter in certain cases upon a stationary stage, while in others shrivelling mercilessly continued. It is also conceivable that the increase in the sedimentation rate was due to disturbance in the albumen/globulin ratio in the serum, which is customary in liver cirrhosis. However, the aforementioned circumstance that the sedimenta-

tion rate decreased to normal values even in the cases in which the liver function steadily grew worse speaks against this.

#### *Diagnosis*

In a number of the cases diagnosis has presented certain difficulties, in that in the beginning splenomegaly or hemorrhagic diathesis was the most pronounced symptom. Sooner or later the liver changes have set their stamp on the clinical picture, however. One of the cases (4), which showed an increased hemorrhagic tendency, was incorrectly diagnosed as Werlhof's disease inasmuch as the number of thrombocytes was greatly decreased, the bone marrow changes coincided with those of Werlhof, and the liver function tests were normal, although certain other symptoms, namely leukopenia and prolonged prothrombin time, did not fit into the Werlhof picture. At splenectomy cirrhotic changes were noticed in the liver. It is of interest that in this case too the sedimentation rate showed a marked elevation (60 mm—80 mm).

#### *Prognosis*

Three of the cases in this group (1, 2, 6) died after a period of illness ranging from two—four years. Five years after the appearance of the first symptoms of the disease a fourth patient (7) is in poor general condition, with very marked icterus and cachexia, and the prognosis here is probably unfavorable. The others (3, 4, 5) after eight, seven and five years, respectively, are in quite good condition and able to lead fairly normal lives. However, they still show slight symptoms of liver damage and therefore the long-run prognosis must be regarded as uncertain.

## **II. Cases with Established or Probable Obstruction in the Portal Vein**

This group consists of seven cases (8—14), four of whom were boys and three girls. The age at which the first symptoms of the disease were noted was considerably lower in these cases than in the preceding group — in two cases at one and three months

respectively, in four cases at one and a half to three years, and in one case at seven years. Hematemesis or melena without previous warning and without previous infectious disease or trauma was the first symptom observed in three cases (8, 9, 12). In three cases enlargement of the spleen had been established in connection with, respectively, septic pharyngitis (10), poliomyelitis (11), and pelvic osteomyelitis (13), all of which probably were of etiologic significance. Finally, in one case (7) the patient had an erysipelas-like infection in one foot when newborn and the abdomen had been distended as far back as the parents could remember. In spite, however, of repeated abdominal examinations, palpation revealed nothing pathological until enlargement of the spleen was established in connection with the first vomiting of blood two and a half years later. Thus an etiological connection between the infection in the first month of life and the later incidence of the disease cannot be definitely established.

Wasserman and tuberculin tests were negative in all cases. The connection between syphilis and Banti's syndrome has been much discussed. Cases with both positive and negative Wassermanns which improved after anti-luetic treatment have been described. The specificity of the seroreaction in some cases of Banti's syndrome may be questioned, however. Of interest in this connection is a case described earlier by one of the authors (LICHENSTEIN 1914) in which a girl whose parents were healthy, with negative Wasserman reaction, had a positive Wasserman before splenectomy which afterwards became negative.

#### *Symptomatology*

All cases showed considerable enlargement of the spleen; after extirpation the spleen weights were noted at between 130 g and 400 g, corresponding to 0.8%—1.4% of the body weight. Thus they were four to six times larger than normal. It has been pointed out that noticeable variation in the size of the spleen in connection with hemorrhages is a characteristic feature of so-called thrombophlebitic splenomegalies, above all in children, while this symptom is less marked in adults, probably because

splenic sclerosis increases with age. The phenomenon is not, however, pathognomonic for this form of Banti's syndrome but is also found in splenomegalous hepatic cirrhosis with portal hypertension (BRANDBERG 1935). A noticeable reduction in the volume of the spleen in connection with hematemesis and a subsequent increase in the blood-free interval has been established in only two of our cases (9, 11) but was very obvious in one of these.

In all cases except one (8), in which we have no information on the point, the spleen was examined microscopically after extirpation. In all of these an increase in the connective tissues in the capsule and trabeculae and sclerosis of the pulp was found — in other words, fibroadenia. In a few of the cases the spleen also showed hyperemia; in one case (9) a small thrombus was found in one of the vessels. The malpighian bodies were strikingly large in three cases but their number had not increased. The microscopic changes coincided with those usually found in Banti's syndrome and there is no difference in principle in this respect between the different forms, as is also pointed out by BRANDBERG 1935, THOMPSON 1940, and KELSEY and ASSOCIATES 1947.

There was considerable *anemia* secondary to the hemorrhages in all cases, and in a few cases extremely low values with hemoglobin c. 3.5 g % and 1—1.5 million red blood corpuscles were noted. As a rule the anemia was fairly resistant to treatment and the blood values returned to a more normal level only slowly. In two cases (9, 11) slight anemia could be established even before there were any hemorrhages. In four cases (8, 9, 11, 12) there was moderate *leukopenia* of between 3 000 and 5 000, and there was slight *thrombocytopenia* in at least four cases (8, 11, 12, 13). These changes disappeared completely after splenectomy. Differential count has not revealed any noteworthy conditions.

*Sternal puncture* was undertaken in every case but one (8) and usually, as in the splenomegalous cirrhoses, showed a marrow rich in cells without specific features. In a few cases (12, 13), on the other hand, the specimen was relatively poor in cells.

As with the preceding group, the examination is without diagnostic value.

There was no *icterus* in this group. Increased blood destruction was indicated in only two cases (11, 14) by a slight rise in the *icterus* index to 1:10 to 1:12, a faintly positive indirect Hijman van den Bergh reaction, and slight urobilinuria. In all cases but two (8, 10) the osmotic resistance of the blood corpuscles was tested and found to be normal or slightly increased.

The symptom which, with enlargement of the spleen, characterized the clinical picture in these cases more than any other was the repeated *gastroesophageal hemorrhages* in the form of hematemesis or melena. In one case the course was characterized by almost constant anemia as a result of the occult bleeding. In all cases *esophageal varices* could be shown roentgenologically. Sometimes the hemorrhages came in connection with fevers such as measles or common colds, but equally often without any ascertainable reason. Their frequency varied widely, not only from case to case but also at different times in the same patient, and hemorrhage-free intervals of up to several years were not unusual, a circumstance which should be kept in mind when the therapeutic results are appraised.

In two cases (9, 11) which on one or more occasions had repeated alarming hemorrhages these were followed by several weeks of *fever*. According to some authors such "post-anemic" fevers indicate progressive thrombosis. The majority, however, regard them as resorption fevers.

In at least one of the patients in this group the existence of a welldeveloped *hemorrhoidal plexus* was established. As far as could be seen no large hemorrhage had arisen therefrom. It is a curious fact, which has also been pointed out in the literature, that patients with portal hypertension bleed almost exclusively from their esophageal and gastric varices and seldom from other collateral vessels. Hence BARONOFSKY and WANGENSTEEN (1945) think it probable that the hematemesis is not, as is usually assumed, due to rupture of the varices but to an erosion of the hyperemic mucous membrane by the gastric juice, and they consider that they have confirmed this by experimental inves-

tigations. PHEMISTER and HUMPHREYS (1947) have at any rate shown in one case in which total gastrectomy was carried out that severe hematemesis may have its origin in diffuse bleeding from the mucous membrane of the stomach.

There was a distinctly *widened vein net* in the abdominal wall in two cases. This sign has been considered an indication of obstruction in the common portal vein. The correctness of this could not be confirmed, since upon splenectomy no obstacle could be shown in these cases.

There was *ascites* in five cases in this series (8—11, 14) showing the characteristic intermittent behaviour which has been emphasized particularly by WALLGREN (1927). Signs of ascites appeared shortly after the hemorrhages ceased and then gradually disappeared. According to WALLGREN, this phenomenon is due to a temporary increase in the pressure in the portal or splenic vein which arises after the damaged varices have become thrombosed and before new collateral circulation has been opened. A relatively high degree of ascites is generally considered indicative of occlusion of the common portal vein. The position of the obstruction could be established in only two of our five cases with ascites; in both it was located high up in the common portal vein. The absence of ascites does not, on the other hand, exclude such a localization, as is indicated by another case (13).

As far as one can judge from this series ascites in occlusion of the portal vein or its tributaries has not the same prognostic significance as in hepatic cirrhosis, in which it probably has an at least partially different origin. The two patients who were followed longest are still alive twentyfour and seven years, respectively, after the symptom first appeared. Furthermore, the first of these had ascites for the last time twentytwo years ago.

In two cases belonging to this group there was a *general hemorrhagic tendency* in the form of a tendency to cutaneous hemorrhages (8) and hematuria (11). The prothrombin time was determined in all cases but one (8) and showed without exception normal values (< 25 sec.). The bleeding time and clotting time were slightly prolonged in one case (8).

There have been no signs of any extensive *liver damage* in

the cases in this group. In three cases slight enlargement of the liver was found in the beginning; later this disappeared. In all cases the liver was found in connection with splenectomy to be of normal size and appearance. Upon further examination in connection with the making of a portacaval anastomosis, however, a firmer consistency of the liver was ascertained in one case, and upon microscopic examination signs of chronic hepatitis were found. Hence a complete examination of these cases should include liver biopsy; this seems to have been the case only exceptionally (ROUSSELOT 1940). Liver function tests were made in all cases. In two of them Takata's reaction was positive, and judging by the function tests, there was certain liver damage in four cases in all in this group (9, 11, 12, 14), even if it was not sufficiently marked to give rise to clinical symptoms.

In the description of hepatic cirrhoses the increased *erythrocyte sedimentation rate* was mentioned as an important and hitherto disregarded symptom. In the cases with established or probable obstruction in the portal vein the sedimentation rate was normal except in a single one (14) in which there was a constant elevation to about 40 mm. It was in this case, moreover, that biopsy revealed signs of chronic hepatitis.

#### *The Nature of the Portal Obstruction*

In many cases with the typical clinical picture of a portal bed block one fails to demonstrate at splenectomy the site and nature of the obstruction. This does not indicate that there is no such block, since the portal region is very difficult to survey. Because of this WALLGREN (1927) proposed the term pylephlebostenosis instead of portal or splenic vein thrombosis, which was used previously.

Cases have also been described in the literature, however, in which even autopsy failed to reveal an obstruction in the portal circulation, as KAIJSER (1934), among others, has pointed out. BRANDBERG (1935) and THOMPSON (1940), on the other hand, have declared that in all cases subjected to complete and thorough examination a mechanical explanation of the stasis was found. Recently KELSEY and ASSOCIATES

(1947) made a summary of sixtyone cases of chronic portal vein disease demonstrated at autopsy. Their material, which included only adults, indicated that the most common change was a thrombosis which was limited only in a few cases to the common portal or splenic vein. Phlebosclerosis and neoplastic invasion were noted as among the other causes of stenosis of the portal vein. In the majority of thrombosis cases one or more etiological factors could be established, such as inflammation, particularly in the abdominal organs, traumata, and surgical intervention in the abdomen.

In children, and especially those cases in which the disease shows itself at an early age, one must take into consideration not only thrombosis but also the possibility of some developmental anomaly affecting the portal vein or a progression of the normal thrombotic process in the umbilical vein. According to THOMPSON (1940), stenosis of the portal vein could be established in all of four cases which showed clinical signs of congestive splenomegaly in early infancy and which underwent autopsy.

No obstruction in the portal vein could be observed or palpated in connection with splenectomy in any of our cases. Three later underwent a new operation, however, and in two of these (11, 14) the wall of the common portal vein showed a fibrous thickening, and the pressure here seemed to be very low, indicating that the obstruction extended peripherally. The changes corresponded to those which might be expected to be induced by a previous thrombosis. In the third case (13) the portal wall was again thickened, but the vein had a number of lumina several of which contained fresh thrombi. Here the picture corresponded most closely to what has been called cavernomatous transformation of the portal vein. According to WHIPPLE (1945) the reasons for this have been much discussed; among the possibilities suggested have been an earlier thrombosis with recanalizations, a teleangiectatic granulation tissue, or a congenital malformation.

In all of the cases in our series in which the portal vein was subjected to thorough examination with freeing of the vessels in the hepatoduodenal ligament, it has thus shown itself to be pathologically changed. Since the other cases showed on the whole the same clinical picture, there were probably similar pathological changes in them. What has been said in the fore-

going clearly indicates that one cannot exclude the presence of a portal obstruction after mere inspection or palpation of the available parts of the portal or splenic vein. According to BLAKEMORE (1947), pressure determination in the different branches and venography following injection of contrast medium are very useful in establishing the localization of an extrahepatic portal block.

#### *Diagnosis*

It is generally regarded as impossible to make the clinical diagnosis of an obstruction in the portal or splenic vein when gastroesophageal hemorrhages are absent (PFAUNDLER-SCHLOSSMAN). Hence a case from our clinic reported in 1935 by STRÖM is of great interest in this connection; in this case obvious variations in the size of the spleen in combination with changes in the blood picture led to the diagnosis of stenosis of the splenic vein in spite of the absence of hemorrhages. Upon operation (splenectomy) the splenic vein was found to be surrounded by enlarged lymph glands which were assumed to have brought about intermittent stenosis of the vessel. Later it was shown that the patient had Schaumann's disease.

In our series three cases had no gastroesophageal hemorrhages in the early stages of the disease. In one of these (10) the diagnosis of anemia was made and in another (11) constitutional thrombocytopenia. The true nature of the disease was not made clear until after the onset of hemorrhages. In the third case (13) the diagnosis of portal thrombosis was made from the beginning on the basis of the history and clinical symptoms.

When there are gastroesophageal hemorrhages the diagnosis is easy to make if the spleen is distinctly enlarged. In some cases, however, as has been said, splenomegaly may be difficult to establish immediately after a hemorrhage, and under such circumstances the cause of the latter may easily be misinterpreted. This happened in two of our cases. In one (9) hematemesis was assumed the first time it occurred to be due to blood swallowed from the naso-pharynx. In the other (12) the child was cared for at home for several weeks under the diagnosis of ulcer of the

stomach. The correct diagnosis was not made until the hemorrhages recurred. In all the cases in this group esophageal varices could be established roentgenologically, although in one of them (12) only after splenectomy. This important method of examination should never be neglected when portal hypertension is suspected.

### Differential Diagnosis

In this connection we shall confine ourselves to a discussion of the differential diagnosis between the different types of Banti's syndrome. So-called idiopathic enlargements of the spleen seem to be very rare in childhood and therefore may probably be safely ignored. Hence the chief problem in differential diagnosis is to decide between *splenomegalous hepatic cirrhosis* and *chronic portal vein disease* (portal obstruction). The former is not difficult to diagnose when there are distinct signs of hepatic disease. But there are all intermediate stages, from these cases which perhaps should not be included in the Banti group to those in which enlargement of the spleen at least in the beginning completely dominates the picture. On the other hand, there are many cases of chronic portal vein disease in which the liver also shows signs of being affected. Whether the liver damage in these cases is primary or secondary in relation to the changes in the portal vein is a very significant question, but as yet it cannot be answered. ROUSSELOT (1940), who followed his cases with repeated biopsies over a period of several years, has shown that extrahepatic obstructions in the portal circulation can occur without any signs of simultaneous affection of the liver.

In the other group in our series there were no clinical signs of hepatic disease (icterus, urobilinuria). Aside from this there are a number of differences between the two groups which could be considered to have a certain differential diagnostic significance (see Table I).

In the cirrhosis cases the onset of the disease was gradual and marked by fatigue and lack of appetite, in some cases icterus and epistaxis as well. In cases with established or probable obstruction of the portal vein the onset of the disease was usually

characterized by sudden hematemesis with no preceding subjective symptoms. The later course also varied in the two groups. In cases without hepatic cirrhosis the picture was dominated by repeated *gastroesophageal hemorrhages*; these occurred in only one of the cirrhosis cases and then only shortly before death. Corresponding to this, *esophageal varices* were established in all the cases in Group II but only in the aforementioned case in the cirrhosis group. In BRANDBERG's (1935) material, which included for the most part only adults, hematemesis was usual in splenomegalous hepatic cirrhosis; of four children two had this symptom, both at a relatively early stage in the disease. Even if such early gastroesophageal hemorrhages are chiefly suggestive of an obstruction in the portal vein, hepatic cirrhosis cannot be excluded.

There was *ascites* in both groups. In cases with established or probable portal obstruction it was a common symptom which appeared at any time in the course of the disease, had a typically intermittent character, and was interpreted purely as a stasis phenomenon. In the cirrhosis cases, on the other hand, the ascites developed late and had a more permanent character. When there were no other signs of portal stasis it was regarded principally as an expression of a disturbance in the liver metabolism and was prognostically an unfavourable sign.

*Blood changes* in the form of anemia, leukopenia, and thrombocytopenia occurred in both groups. The anemia was most pronounced in cases with portal obstruction, due to the hemorrhages in those cases. Leukopenia was established to about the same extent in both groups, while thrombocytopenia was most constant in the cirrhosis cases. On the whole, blood examination does not seem to yield information of any particular value in differential diagnosis between the two groups.

A *prolongation of the prothrombin time* was a common symptom in the cirrhosis cases but was not found in any case belonging to the other group, even though there sometimes were other signs of impaired liver function. Prolongation of the prothrombin time is thus a symptom of severe liver damage and as such a valuable aid to diagnosis. A normal prothrombin time does

Table I.

*Differential diagnosis between splenomegalous hepatic cirrhosis (1—7) and splenomegaly with established or probable obstruction in the portal vein (8—14).*

Case No.	Sex	Age at Onset of Disease Years	Icterus	Urobilinuria	Esophageal Varices	Hematemesis	Ascites	Prolonged Prothrombin Time	Increased Sedimentation Rate
1	♂	8	+	+					
2		7	+	+					
3		11	+	+					
4		5	+	+					
5		6	+	+					
6		11	+	+					
7		8	+	+					
8		3	+	+					
9		1 <sup>1/2</sup>	+	+					
10	♂	1 <sup>1/2</sup>	+	+					
11		1 <sup>1/2</sup>	+	+					
12		7	+	+					
13		3 <sup>1/2</sup>	+	+					
14	♂	2 <sup>1/2</sup>	+	+					

not exclude the possibility of hepatic cirrhosis, however. A general hemorrhagic tendency was more common in the cirrhosis cases, to which probably both the prolongation of the prothrombin time and the more constant thrombocytopenia in these cases contributed.

Our experience indicates that the *erythrocyte sedimentation rate* is of considerable value in differential diagnosis. Particularly in the earlier stages of the disease the sedimentation rate was increased in all the cirrhosis cases, while in all the cases in the other group except one it remained normal.

As has already been said, *liver function tests* turned out positive to a slight extent even in a number of cases with established or probable obstruction in the portal vein. In view of the uncer-

tainty attendant on evaluation of these function tests and the absence of clinical symptoms of hepatic disease, we have for the time being thought it best to exclude these cases from the splenomegalous hepatic cirrhosis group. The differences between the two groups in clinical picture and course seem to justify the classification adopted here from the practical clinical point of view.

### Therapy

*Survey of Literature.* Treatment in Banti's syndrome is directed primarily toward the combatting of portal hypertension and its sequel, i. e. hemorrhages from esophageal varices, and up to recent years it has consisted mainly of *splenectomy*. The operation has been justified on the grounds that through splenectomy the supply to the portal circulation is diminished by up to 40 %, thus effecting a considerable reduction in pressure. In the case of an isolated block in the splenic vein between the spleen and the confluence with the coronary vein the operation would have a curative effect. In cases without signs of portal stasis, the primary object has been to combat such troublesome symptoms for the patient as anemia and icterus, insofar as these are due to increased blood destruction. In many cases it was possible to establish a retrogression in the blood changes, including leukopenia and thrombocytopenia, after extirpation of the spleen, a circumstance which lends support to the assumption that the spleen has an inhibitory effect on the bone marrow activity.

Even though in a number of cases of *splenomegalous hepatic cirrhosis* good results from splenectomy were reported, the operative mortality, particularly in adults, is alarmingly high. It has also been objected, by BRANDBERG (1935) for example, that in many cases the observation period was altogether too short in view of the markedly chronic course of the disease to permit a decision as to the value of the operation.

According to BARTHELS (1944) the prognosis is decidedly poor, both in children and adults. In opposition to this, however, PEMBERTON and KIERNAN (1945) have noted satisfactory results even in many cases with advanced liver damage. In addition to retrogression of the anemia

and leukopenia, these two recorded frequent improvement in liver function following splenectomy; the effect on the hemorrhages, on the other hand, was usually poor.

Even in cases with *obstruction in the portal or splenic vein* varying results from splenectomy were reported, in part due to the nature of the material and length of the observation period. In general the prognosis is said to be better for children than adults. The primary mortality is at any rate considerably lower in these age groups.

Thus WALLGREN (1927) noted good results in all three of his cases. In two of these, however, the observation time did not exceed two years, and the author himself made a very cautious prognosis.

In 1934 KAISER summarized the cases of portal or splenic vein thrombosis (among them WALLGREN's) which had been published up to that time. With the author's three personal cases, the material consisted of thirtyone children and as many adults. Of the first-named group, four died in connection with splenectomy (intestinal infarction, shock, pneumonia); in six the hemorrhages continued even after the operation, with one death; and for the rest good results were reported. Five of the latter had been followed up at most one year, however, and in eight cases no information was given as to the length of the observation period. Of the adults, sixteen died immediately upon operation and four later as a result of hemorrhages or progressive thrombosis; good results were reported for the remainder. In this group also, however, the observation period was altogether too short in the majority of cases.

Of BRANDBERG's cases (1935), eleven were children and eighteen adults. Of the former three died in connection with splenectomy and three later, while five were in good health twelve, nine, six, two, and two years after the operation. Of the adults eight died immediately and seven later, while three were free of symptoms fourteen, six, and four years after the operation.

BARG and DULIN (1940) have reported on forty three cases of Banti's syndrome, half of which were splenectomized and half not. Their account fails to indicate the diagnostic criteria adopted by these authors. Hematemesis had occurred in almost half of the cases and epistaxis in a fourth. Of twentytwo who underwent splenectomy, six died in connection with the operation, four were symptom-free two—nine years later, and two were considerably improved after three years and one year, respectively, being troubled only by fatigue. During the observation period (ten and five years, respectively) two had relatively small hemorrhages. Of five patients with preoperative hemorrhages, two continued to bleed

after splenectomy, while four did not have this symptom until after the operation (three of these died). Of twenty one who were not operated upon, six were alive and eleven dead (so far as is known) at the time of publication.

In 1940 ROUSSELOT reported the results of splenectomy in fifteen cases of congestive splenomegaly with hematemesis but no indication of hepatic cirrhosis either upon operation or later. In nine cases (seven children) the hemorrhages continued, and six of these (four children) died after a period varying from thirteen months to three days. In six cases (four children) the hemorrhages ceased immediately after splenectomy (observation periods nineteen, thirteen, six and a half three, and two years; ten months). According to this author, the site of the obstruction (the common portal or splenic vein) and anatomical conditions, which may vary in different patients (superior mesenteric vein opening into the splenic or portal vein etc.), play a decisive part in the result.

As the above shows, the late results of splenectomy have on the whole been disheartening. Hence attempts have been made to find other ways of combatting the portal hypertension and its bad effect. The methods which have been most used hitherto are *omentopexy* according to TALMA-MORRISON and *ligature of the stomach veins*. The former seems to have given encouraging results only in exceptional cases, while according to WHIPPLE (1945) the results of ligature of the veins to the cardia and esophagus have actually been disappointing.

The first attempts to treat esophageal varices by *direct injections of sclerosing agents* was made in 1939 by CRAFOORD and FRENCKNER.

These authors treated a case of Banti's syndrome which had continued to bleed after splenectomy with good result, in that there were no new hemorrhages during the observation period (three years) and the x-ray picture of the esophagus became normal. Using the same method, MOERSCH (1947) obtained satisfactory results in about half of the cases in his series, including twenty two patients with Banti's syndrome who were splenectomized previously; the length of the observation period varied from three to seven years. Gastroscopy revealed the majority of the unsuccessful cases to have varices in the upper part of the stomach, and according to the author the presence of these indicates that the treatment should not be attempted.

BARONOFSKY and WANGENSTEEN (1945) have undertaken extensive

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*gastrectomy* in two cases of Banti's syndrome, one with and one without hepatic cirrhosis, and obtained satisfactory results in both; the length of the observation period is not stated, however. PHEMISTER and HUMPHREYS (1947) carried out a fairly successful total gastrectomy in one case of Banti's syndrome which continued bleeding after splenectomy and injection treatment of the varices and a successful gastroesophageal resection in another previously splenectomized case. The observation period was two years and eight months for the former and three and a half months for the latter.

Portal hypertension has long attracted particular interest at the Spleen Clinic in New York (WHIPPLE and ASSOCIATES). After it became clear that extirpation of the spleen gave lasting results only in a limited number of cases, efforts were made to find a more effective method of treatment. The method finally adopted consisted of *shunting of the portal blood into the caval circulation, by-passing the block in the liver or portal vein.*

To be sure, attempts to relieve the pressure in the portal circulation by means of a so-called Eck fistula (i. e., direct anastomosis between the portal vein and the inferior vena cava) had been made off and on as early as the beginning of the century (VIDAL 1903) but virtually without success.

The first encouraging results were obtained with the BLAKEMORE-LORD technique (1945) consisting of non-suture anastomosis with vitallium tubes. Recently (1947) BLAKEMORE reported on twenty three cases of Banti's syndrome with hypertension in the portal vein in which portacaval anastomosis was carried out using this technique. The material included cases with both extra- and intrahepatic block. Fifteen patients underwent *splenorenal anastomosis following splenectomy and left nephrectomy* (in one the spleen had been removed earlier). Two of these died of, respectively, cholemia and mesenteric thrombosis soon after the operation. *Direct end-to-side portacaval anastomosis* was employed in seven cases, with two deaths (bleeding, hepatic insufficiency). Seventeen of the nineteen survivors have been followed up for more than six months. In the portacaval cases no bleeding has occurred during the observation period. In eight of the cases with splenorenal shunt, bleeding recurred after the operation. Two of these died: one, a child with portal cirrhosis, of uremia (polycystic disease of the kidney); and the other, a man with portal cirrhosis, as a result of cholemia. In the case of the child, autopsy showed that the anastomosis had been obliterated; in the second case it was patent. In three of the six remaining cases the later course indicated that the anastomosis was function-

ing, but in three it appeared to have been obliterated. Pressure readings taken at operation before and after the anastomosis was made indicated that the splenic vein was not always sufficiently wide to permit reduction of the pressure in the portal vein to normal.

With regard to the indications for the operation, BLAKEMORE asserted in an earlier work (1946) that portacaval anastomosis was indicated in cases of hepatic cirrhosis in which the operative risk seemed to be relatively slight; and in all cases with extrahepatic block except those in which the block was located only in the splenic vein peripherally to the confluence with the coronary vein, in which splenectomy would suffice. Frequently the type of anastomosis which should be employed can be decided only on the operating table, and for this purpose pressure readings in the portal vein and its tributaries and venography following injection of a contrast medium are of great value in establishing the site of the block.

LINTON and ASSOCIATES (1948) prefer *end-to-side splenorenal anastomosis following splenectomy with preservation of the kidney* to the shunt types described by BLAKEMORE. They consider this operation preferable to the direct portacaval anastomosis partly because it is easier technically, partly because simultaneous extirpation of the spleen reduces the quantity of blood which has to pass through the portal vein by up to 40 %, and partly because only a part of the blood is led past the liver, thus diminishing the danger of disturbances in the liver metabolism. They consider that preservation of the kidneys lessens the risk of complications connected with kidney functions and tends to counteract thrombosis in the anastomosis. Experimental investigations by JOHNS and BLALOCK (1947) also indicate that an end-to-side anastomosis has better prospects of remaining patent than an end-to-end anastomosis in which the kidney is removed. The authors prefer BLALOCK's *suture method* to BLAKEMORE's non-suture method, since Blalock has demonstrated by experiments on animals that the danger of thrombosis is greater in the non-suture method.

The following operation results are reported by LINTON and ASSOCIATES. Seven out of eight patients with extrahepatic block had no bleeding after the operation; here the observation period varied from five to twentytwo months. In five cases splenectomy and end-to-side splenorenal anastomosis were carried out; there were no bleeding episodes during five—fourteen months. In the other three cases splenectomy had been done previously, wherefore recourse was had to anastomoses between other branches of the portal vein or the vena cava. In one of these, in which the inferior mesenteric vein was anastomosed to the left suprarenal vein, bleeding episodes recurred after four months. There were no deaths in the extrahepatic group. On the other hand, out of seven patients with intrahepatic block only two survived operation.

One of these was observed for twenty nine months after the operation, which in this case consisted of an end-to-end splenorenal anastomosis with vitallium tube, and during the whole period the patient had no hemorrhages. In the other case the observation period was only two months. Of the five who died in connection with the operation, two had undergone splenectomy and end-to-side splenorenal anastomosis, while the other three had been subjected to direct anastomosis of the portal vein (superior mesenteric vein to the inferior vena cava). All were in poor condition, with symptoms of serious hepatic lesion; the average age in the intrahepatic group was also considerably higher than in the extrahepatic. In the great majority of cases in both groups esophageal varices were still visible on the x-ray picture.

The *symptomatic* treatment in portal hypertension with gastroesophageal hemorrhages consists of blood transfusions and administration of iron, liver, etc. According to TOCANTINS (1948) only enough blood should be given to maintain circulation in order to avoid fresh hemorrhages resulting from a rise in blood pressure. ROWNTREE (1947) has employed esophageal tamponade in a few cases and considers that it may have a life-saving effect.

#### *Operative Results in Our Own Cases*

One of the seven cases in the first group was splenectomized following faulty diagnosis of Werlhof's disease. After operation the leukopenia and thrombocytopenia disappeared and now, five years later, the girl is in good condition. None of the others has undergone operation.

In all seven of the Group II cases in our series there has been *splenectomy*, in six cases as an isolated measure. In the last case (11) a splenorenal anastomosis according to BLAKEMORE was made simultaneously (5/12/47). Because in the last-mentioned case it was for technical reasons considered relatively improbable from the very beginning that the anastomosis would function, this operation may in view of the result be compared with the isolated splenectomies.

As Table II shows, the results of splenectomy were extremely discouraging, in that all the patients continued to have hemorrhages after the operation.

*Table II.*

Results of splenectomy in seven cases with established or probable block in the portal vein.

Case No.	Sex	Age at Onset of Hemorrhage	Age at Splenectomy	Results	Period of Observation
8	♀	3	7 <sup>1/2</sup>	Bleeding after 1 month.	22 years; then new op.
9	♂	1 <sup>1/2</sup>	4 <sup>1/2</sup>	Bleeding after 2 years.	8 years
10	♂	2	2	Bleeding after 2 years.	4 <sup>1/2</sup> years
11	♀	4	4 <sup>2/12</sup>	Bleeding after 7 months.	10 months, then new op.
12	♂	7	8	Bleeding after 1 month.	4 years
13	♀	5	5 <sup>1/2</sup>	Bleeding after 1 month.	3 years; then new op.
14	♂	2 <sup>1/2</sup>	2 <sup>1/2</sup>	Bleeding after 6 months.	1 <sup>1/2</sup> years; then new op.

In three of the cases bleeding episodes recurred as early as within one month; the others were symptom-free from six months to two years before hemorrhages recurred. One of the patients bled several times during the year following splenectomy but has been free of symptoms since (observation period four years). The others still bleed at varying intervals but are in relatively good condition between times. All the cases still show esophageal varices in the x-ray pictures. In the cases in which there were leukopenia and thrombocytopenia before splenectomy these have disappeared.

Upon splenectomy one of the patients (11) was in poor condition, with severe anemia which had defied all treatment, but she stood the operation surprisingly well. The others were in relatively good general condition when the spleen was extirpated and the postoperative course was free of complications in all cases. Thus our material confirms the information given in the

literature as to the low primary mortality in splenectomies on children.

On the other hand, the late results in our cases have been considerably worse than in the material published elsewhere. This circumstance may in part be due to the fact that in the latter the observation period has frequently been too short. When this has not been the case one presumes that the block to the portal flow was localized in such a way (the splenic vein between the coronary vein and the spleen) that splenectomy had a curative effect.

In one case (8) *Talma's operation* was carried out twentytwo years after splenectomy. Previously the patient was treated over a long period with injections into the esophageal varices, but these had at best a transitory effect. In this case Talma's operation also failed to bring about any improvement.

Three cases (11, 13, 14) were operated on with *anastomosis between the portal and caval systems*. Only one of them (11) had not been previously splenectomized and was therefore a good subject for a typical Blakemore operation with end-to-end anastomosis between the splenic vein and renal vein following splenectomy and left nephrectomy. Conditions were unfavourable, however, in that the splenic vein plunged into the pancreas after only a few centimeters. Hence the anastomosis kinked the two veins and thereby increased the danger of thrombosis. The later course indicates that obliteration occurred.

Because of repeated serious hemorrhages the patient was operated on again for the purpose of making an Eck fistula. It was discovered, however, that the portal vein had undergone sclerotic changes both in the hepatoduodenal ligament and peripherally to it, making it impossible to lead the blood from the portal area past the block by means of an Eck fistula. Instead an *anastomosis between the coronary vein and the vena cava* was made, accomplishing a direct shunt of the blocked blood in the esophageal varices. Such an operation has never been described before. Because of a certain tension in the anastomosis with the very narrow vessel the chances were not too great, however, that the new anastomosis would remain patent, and half

a year later the patient had fresh bleeding in the form of melena.

In Case 13 splenectomy had been undertaken three years previously without effect. The object was now to attempt relief by means of an Eck fistula. The operation was extremely difficult because of fibrous induration and teleangiectatic changes in the hepatoduodenal ligament. An end-to-side anastomosis between the divided portal vein and the vena cava was made. However, at the site the portal vein was sclerotic and contained a thrombus mass, making it unlikely that the obstruction was successfully circumvented. In spite of very careful dissection of the callous tissues the common bile duct, which must have been extremely fine and thin-walled, was evidently ligated, and the patient had an ieterus which necessitated cholecystogastronomy a week later. She has since had repeated bleeding and a few attacks of cholangitis.

Finally, in Case 14, in which splenectomy had been undertaken one and one half years earlier, a vitallium-tube anastomosis was made regardless between the remainder of the splenic vein and the left renal vein following nephrectomy. The splenic vein, however, was sclerotic, non-elastic, and very fine, and therefore unfavourable for anastomosis. Presumably it did not remain patent, as there was fresh bleeding after only a few months. A further operation was undertaken with the object of attempting a direct anastomosis between the coronary vein and the vena cava; an Eck fistula would not have helped, as the obstruction lay peripherally to the common portal vein. The coronary vein, however, was too thin and fine to permit an anastomosis to function, so nothing could be done.

These cases illustrate primarily the great obstacles in the way of achieving a functioning shunt between the portal and caval systems in cases which have previously undergone splenectomy. A direct anastomosis according to Eck between the common portal vein and the vena cava is best suited to cases of portal hypertension in which the obstruction is intrahepatic, as for example in Laennec's hepatic cirrhosis. Our cases illustrate the difficulties and the poor prospects of success with such an

anastomosis if the changes include the common portal vein and periphery thereof.

The case with the best prospects should have been (11), after the splenorenal anastomosis. The anatomical conditions, with a very short free vein stump, were unfavourable, however. As was said before, the danger of thrombosis is lessened if the kidneys can be saved and an end-to-side anastomosis made, preferably with suture technique. This is shown by the following case, which, although it does not belong to this series because it involved an adult, will be briefly described in order to show the advantages of the method in cases which have not been previously splenectomized.

A forty seven year old woman had been healthy ever since she had hepatitis at the age of fifteen until, the year before admission to the hospital, she had an attack of hematemesis. She was treated for ulcers. X-ray of the stomach was negative, however. After nearly a year the hematemesis recurred. X-ray now revealed extended esophageal varices. In addition she had splenomegaly and leukopenia. Upon operation her spleen, the size of man's head, was removed and followed by a sutured end-to-side anastomosis between the splenic vein and the left renal vein. In the post-operative course she had a few attacks of fever but otherwise the healing was free of complications. Four months after the operation there remain only a few smaller varices in the lowest part of the esophagus. The leukocyte and thrombocyte picture is now normal. Although it is probable that the anastomosis between the portal and caval system made a considerable contribution in this case to reduction of the pressure in the portal system, it must be pointed out that splenectomy alone can for some time give the same clinical results. Only the later course will show finally the value of the anastomosis. Examination four months after the operation showed that both kidneys were functioning normally.

As the above indicates, we still have only limited experience of the new methods of reducing portal hypertension by anastomosis operations between the portal and caval systems. Moreover, two of our cases were not very well suited to such operation, as they had undergone splenectomy earlier.

In our experience direct anastomosis between the vena cava and the portal vein, which has been alleged to give good results in cases of intrahepatic block, is unsuitable when the obstruc-

tion is located in the common portal vein or peripherally to it. If splenectomy has been carried out before, the only course left is to attempt an anastomosis with one of the smaller tributaries, such as the superior mesenteric vein, or, as in our case, directly with the coronary vein. The small dimensions of these vessels increase the risk that the anastomosis will be obliterated by thrombosis. In such cases the situation is desperate. Treatment of the esophageal varices with sclerosing injections has not been recommended if the patient is under ten because of the great risks. Resection of the stomach and lower part of the esophagus as a last resort involves very great risk with only dubious prospects of success.

Thus we have had poor results from anastomosis operations in the cases which were previously splenectomized. Recent reports from the U.S.A. seem to indicate that good results may be expected with end-to-side splenorenal anastomoses. Our success with our own latest case appears to confirm this. Hence we feel that splenectomy should not be undertaken in cases with Banti's syndrome without simultaneous planning of an anastomosis, shunting the blood to the caval system.

In conclusion, however, it must be said that the observation period is still too short to permit final judgement of the value of these new operations.

#### **Summary and Conclusions**

Following an exposition of the term Banti's syndrome, a series of our own cases is reported, seven of them belonging to the group splenomegalous hepatic cirrhosis and seven to the group of cases with established or probable obstruction in the portal vein.

The differential diagnosis between these two groups is discussed. In the former symptoms of liver damage dominate; in the latter, bleeding from the digestive tract, more particularly esophageal varices. An increased erythrocyte sedimentation rate speaks in favor of hepatic cirrhosis. However, there are cases on the border-line between the two groups.

Treatment is directed primarily toward counteraction of the

portal hypertension and its consequences, i. e. bleeding from esophageal varices.

Ordinarily splenectomy causes only temporary improvement. All the cases belonging to the second group in the material reported on here were splenectomized, and all had a recurrence of hemorrhages.

The authors report on the newer surgical methods and on their experiences of four cases (one of them an adult). Splenectomy is not to be recommended in cases of portal hypertension without simultaneous planning of a relief anastomosis between the portal and caval systems. Any more definite decision as to the value of the new methods must, however, be postponed until further experience has been gained and the period of observation has been longer.

#### Résumé

A la suite d'un compte rendu de la notion: «Syndrome de Banti» on rapporte une série de cas personnels: 7 cas appartenant au groupe cirrhose hépatique splénomégalique et 7 appartenant au groupe de cas prouvés ou probables d'engorgement de la veine porte.

Le diagnostic différentiel entre ces deux groupes est discuté. Dans le premier le symptôme de lésion au foie domine; dans le dernier ce sont des hémorragies dans le tube digestif notamment des varices œsophagiennes. Une sédimentation accélérée indique la cirrhose hépatique, il y a cependant des cas transitoires entre les deux groupes.

Le traitement est avant tout dirigé contre l'hypertension de la circulation portale et ses conséquences c.à.d. les hémorragies des varices œsophagiennes.

La splénectomie ne produit habituellement qu'une amélioration de courte durée. Tous les cas du deuxième groupe du matériel présenté ont été traités par la splénectomie et tous ont eu des récidives d'hémorragies.

Les auteurs exposent les nouvelles méthodes chirurgicales et communiquent les expériences de 4 cas (dont un adulte). En cas d'hypertension de la circulation portale on ne doit pas conseiller

la splénectomie sans projeter en même temps un anastomose entre les systèmes porte et cave. Il faut cependant remettre une appréciation définitive de la valeur des nouvelles méthodes jusqu'à ce qu'on ait acquis une plus grande expérience et qu'on ait eu un plus long temps d'observation.

### Zusammenfassung

Nach einer Erklärung des Begriffes, Bantis Syndrom, wird eine Serie eigener Fälle mitgeteilt, von denen 7 zu der Gruppe der splenomegalen Lebercirrhosen und 7 zu der Gruppe der Fälle mit nachgewiesenem oder wahrscheinlichem Hindernis in der Vena portae gehören.

Die Differentialdiagnose zwischen diesen beiden Gruppen wird besprochen. Bei der ersten herrschen die Symptome der Leberschädigung, bei der letzteren Blutungen von Seiten des Digestionstraktes besonders Oesophagusvaricen vor. Eine erhöhte Senkungsreaktion spricht für Lebercirrhose. Es gibt jedoch Übergangsfälle zwischen diesen beiden Gruppen.

Die Behandlung richtet sich zunächst gegen die Portahypertension und deren Folgen, d. h. die Blutungen von Seiten der Oesophagusvaricen.

Splenektomie gibt gewöhnlich nur kurzdauernde Verbesserung. Sämtliche der zweiten Gruppe zugehörigen Fälle des vorliegenden Materials wurden splenektomiert und alle hatten Recidive ihrer Blutungen.

Die Verfasser beschreiben die neueren chirurgischen Methoden und teilen ihre Erfahrungen in 4 Fällen (darunter ein Erwachsener) mit. Splenektomie soll nicht angeraten werden in Fällen von Portahypertension ohne dass gleichzeitig eine entlastende Anastomose zwischen Porta- und Cavasystem geplant wird. Ein sicheres Urteil über den Wert der neueren Methoden muss jedoch aufgeschoben werden, bis man grössere Erfahrung gewonnen und längere Beobachtungszeit gehabt hat.

### Resumen

Siguiendo una exposición del término »síndrome de Banti», se informa sobre una serie de casos, de los cuales siete pertenecen

al grupo de cirrosis esplenomegalia hepática y siete al de casos con obstrucción establecida o probable en la vena portal.

Se discute la diagnosis diferencial entre estos dos grupos. En el primer grupo dominan los síntomas de lesiones del hígado, mientras que en el segundo domina la hemorragia del tracto digestivo, especialmente de varices esofágicas. El aumento del grado de sedimentación eritrocítica habla en favor de la cirrosis hepática. Hay, sin embargo, casos intermedios entre los dos grupos.

El tratamiento se dirige ante todo a impedir la hipertensión portal y sus consecuencias, es decir, la hemorragia de varices esofágicas.

La esplenectomía corriente ocasiona sólo mejoría momentánea. Todos los casos del segundo grupo eran casos esplenectomizados y con recaídas en la hemorragia.

Los autores informan sobre los nuevos métodos quirúrgicos y sobre las experiencias obtenidas en cuatro de los casos (uno de ellos de adulto). La esplenectomía no se recomienda en los casos de hipertensión portal sin una preparación simultánea de anastomosis de alivio entre los sistemas portal y caval. Es necesario sin embargo, dejar para más adelante, hasta que se hayan realizado más experiencias y el período de observación haya sido más largo, un juicio más definitivo sobre el valor de los nuevos métodos.

#### Case Reports

*Case 1.* M. 1015—37. Boy b. 20—10—29. Otitis 1935, otherwise previously healthy. Nov. 37 first signs of fatigue and lack of appetite. Dec. 37 admitted to Medical Department, Kronprinsessan Lovisa's Children's Hospital. Normally developed. Somewhat thin, pale, slightly icteric. Considerable enlargement of the liver and spleen. No ascites. Tuberculin test and Wassermann negative. Sedimentation rate 123 mm. Hgb. 10.2 g%; R.B.C. 3.83 mill.; W.B.C. 8400; thrombocytes 300 000. Diff.: segmented 51.5; eosinophils 2.5; lymphocytes 45.5; monocytes 0.5. Icterus index 1:18. Hijman v.d. Bergh dir. +, indir. weak +. Takata pos. Hemolytic resistance: 0.42—0.26 % NaCl. Göthlin's test (15 min. 50 mm Hg): 40 petechiae. Normal bleeding and clotting times. N.P.N. 23 mg%. Urine: nothing pathological; urobilin and bilirubin  $\frac{1}{2}$ . Stools: Weber test  $\frac{1}{2}$ . Temp. first weeks subfebrile, later afebrile.

General condition gradually deteriorated. Feb. 38 suspected ascites Hgb. 8.0 g%; R.B.C. 3.83 mill.; W.B.C. 5800. Icterus index 1: 13. Hijman v.d. Bergh dir. and indir. +. Takata pos. Sedimentation rate 8 mm. Discharged to home. Diagnosis: acute hepatitis + splenomegaly - ascites. Feb. 39 admitted to Sabbatsberg Hospital: marked icterus considerable ascites: 2500 ml was drained off. X-ray examination of abdomen: considerable enlargement of the spleen; liver rather diminished in volume with numerous uneven granulations on the surface. Hgb 9.1 g%; R.B.C. 2.83 mill.; W.B.C. 6700; thromocytes 75 000. Diff.: nothing noteworthy. Icterus index 1: 55. Hijman v.d. Bergh dir. and indir. +. Takata pos. Sedimentation rate 15 mm. N.P.N. 24 mg%. Hemolytic resistance: normal. Diagnosis: hepatic cirrhosis + splenomegaly + ascites. Died same year at home. No gastroesophageal hemorrhage.

*Case 2.* M. 989—40. Girl b. 5—9—31. Father had jaundice at age of 3. Patient perfectly healthy previously. Dec. 38 first signs of fatigue and icterus. May 39 admitted to hospital in Stocksund. Spleen then just palpable. Icterus index 1: 55, gradually decreasing to 1: 9. Diagnosis: subchronic hepatitis. Thereafter relatively well. Autumn 40 again deterioration with fatigue, lack of appetite, and jaundice. Nov. 40 admitted to Medical Department, K.L.C.H. General condition unaffected, good nutrition. Distinct icterus, a number of bruises. Spleen considerably enlarged, liver on X-ray picture rather small. No ascites. X-ray of esophagus: no varices. Temp. normal. Sedimentation rate 56 mm. Tuberculin test neg. Hgb. 12.3 g%; R.B.C. 3.78 mill.; W.B.C. 4900; thromocytes 72 000. Diff.: nothing noteworthy. Sternal puncture (Segerdahl): specimen rich in cells, nothing definitely pathological. Bleeding time 8.5 min.; coagulation time 6.5 min.; coagulum retraction slightly delayed. Prothrombin time 47 sec. Hemolytic resistance: 0.38—0.28 % NaCl. N.P.N. 26 mg%. Icterus index 1: 55. Hijman v.d. Bergh dir. and indir. ++. Urine: urobilin +++, otherwise nothing pathological. Stools: Weber test −. Diagnosis: hepatitis + splenomegaly. Discharged for x-ray treatment of the spleen. Jan. 41 again admitted for check-up. Still enlargement of the spleen and icterus. Sedimentation rate 43 mm. Wassermann neg. Hgb. 11.2 g%; R.B.C. 3.57 mill.; W.B.C. 4200; thromocytes 165 000; reticulocytes 34 %. Diff.: stabs 1; segmented 58; eosinophils 1; lymphocytes 40. Bleeding and coagulation times normal. Prothrombin time 40 sec., hardly affected by Vitamin K treatment. Icterus index 1: 40. Hijman v.d. Bergh dir. trace, indir. +. Takata pos. Urine: urobilin ++, bilirubin—. During the following year relatively good condition. Constant enlargement of the spleen. No signs of ascites. No roentgenologically demonstrable esophageal varices. No anemia but moderate leukopenia and thrombocytopenia. Lowest icterus index value 1: 14. Takata constantly pos. Prothrombin time 25 to 40 sec. Sedimentation rate slowly decreasing to normal values

(10 to 15 mm). — Toward the end of 42 rapid decline. Readmitted 23—11—42: thin, very icteric, slightly cyanotic and dyspneic after exertion; clubbed fingers. X-ray examination of abdomen: size of liver and spleen unchanged. Electrocardiogram: myocardiac damage. Hgb. 13.1 g%; R.B.C. 4.98 mill.; W.B.C. 4800; thrombocytes 85 000; reticulocytes 10 %. Diff.: nothing noteworthy. Prothrombin time 65 sec. Sedimentation rate 12 mm. Icterus index 1: 100. Hijman v.d. Bergh dir. ++, indir. +++. Takata pos. Urine: urobilin +++, bilirubin +++. Stools: Weber test ++. Ascites set in and patient died 15—12. Autopsy (Wilton): spleen considerably enlarged (400 g) with firm consistency; cut surface covered with white dots size of a pinhead. Liver much shrivelled (540 g) with numerous small granulations. The microscopic picture coincided well with that in cases of cirrhosis.

*Case 3.* M. 1048—40. Boy b. 20—5—29. An uncle died of pernicious anemia. The patient was perfectly healthy previously except for acute sore throat at one time. Nov. 40 fatigue, repeated epistaxis. Admitted Dec. Medical Department, K.L.C.H. Tall boy, neither fat nor thin; some small petechiae in the skin. Liver and spleen not palpable but slight enlargement of the liver on roentgenogram. Tuberculin test negative. Temp. afebrile. Sedimentation rate 54 mm. Hgb. 10.7 g%; R.B.C. 3.53 mill.; W.B.C. 4400; thrombocytes 62 000; reticulocytes 15 %. Diff.: stabs 2.5; segmented 42.5; eosinophils 1.5; lymphocytes 46; monocytes 7.5. Sternal puncture (Nordenson): specimen rich in cells, probably damage to formation of thrombocytes. Bleeding and clotting times normal. Prothrombin time 19 sec. Icterus index 1: 12. Hijman v.d. Bergh dir. trace, indir. +. Takata pos. Galactose test: 7 g excreted. Urine: urobilin +++, otherwise nothing pathological. Stools: Weber test neg. April 41 discharged to home in relatively good condition. Diagnosis: hepatic cirrhosis + thrombocytopenic purpura. Thereafter the patient was subjectively well and had no hemorrhagic tendencies. Admitted several times for check-up examinations, most recently June 43. In the beginning subicteric with icterus index at most 1: 36, later sinking to 1: 21. No enlargement of the spleen. X-ray: smaller liver shadow. No ascites. Sedimentation rate: gradual lowering to normal values. No anemia but a tendency to leukopenia (3300 to 8700) and thrombocytopenia (65 to 200 000). Prothrombin time varying between 25 and 75 sec., little influenced by Vitamin K. Bleeding and clotting times normal. Hemolytic resistance: 0.44—0.30 % NaCl. Takata constantly pos. Galactose test: 2 to 3 g excreted. Urine: urobilin +++, bilirubin  $\frac{1}{2}$ . — Check-up examination Feb. 46. General condition good, no icterus, no hemorrhagic tendency. Liver and spleen not palpable; liver shadow rather small on x-ray picture. No ascites. No esophageal varices. Sedimentation rate 3 mm. Wassermann neg. Hgb. 13.7 g%; R.B.C. 4.42 mill.; W.B.C. 3500; thrombocytes 70 000; reticulocytes 6 %.

Diff.: stabs 11; segmented 39.5; eosinophils 1; lymphocytes 44; monocytes 4.5. Sternal puncture (Nordenson): markedly reactive marrow without specific features. Prothrombin time 21 sec. Hemolytic resistance: 0.42—0.30 % NaCl. Icterus index 1: 16. Hijman v.d. Bergl dir.  $\div$ , indir. +. Takata pos. Thymol test 26 units. Serum cholesterol 197 mg%. Phosphatase 12 units. Urine: urobilin +++, bilirubin  $\div$ .

*Case 4.* M. 812—43. Girl b. 6—5—36. Well previously. June 4: first signs of fatigue, lack of appetite, and epistaxis. Given iron treatments without effect. Spring 43 abdominal circumference larger and patient easily bruised. Admitted Sept. 43 Medical Department, K.L.C.H. Pale, with widened vein net in the abdominal wall. No icterus. Liver and particularly spleen enlarged. No ascites. Sedimentation rate 70—80 mm. Temp. afebrile. Hgb. c. 11.0 g%; R.B.C. c. 4.0 mill.; W.B.C. 3700—6700 with c. 50 % lymphocytes; thrombocytes 45 000—165 000; reticulocytes 10—17 %. Prothrombin time 35—45 sec., slight decrease after Vitamin K. Bleeding time 2.5 min., coagulation time 8 min., coagulum retraction normal. Wassermann and tuberculin test neg. Urine: urobilin +++. Galactose tolerance test: 0.6 g excreted. Sternal puncture (Nordenson): conditions as in Werlhof. X-ray of esophagus: no varices. Diagnosis: Werlhof's disease. 26—10—43 splenectomy (Hindmarsh): liver not enlarged but firmer than normal and granulated. Spleen considerably enlarged (500 g) but otherwise normal in appearance. No signs of thrombosis anywhere. Microscopic examination of the spleen (Bergstrand): increased amount of reticulae; lymphoid tissues in Malpighian bodies abundant with large reaction centers; nucleated cells very prominent; among these numerous mononuclears with eosinophilic granula. No iron pigment. — Check-up in out-patient department March 44: general condition good. Sedimentation rate 12 mm. Hgb. 13.3 g%; R.B.C. 4.34 mill.; W.B.C. 13 000; thrombocytes 296 000. Since 46 occasional abdominal pain and periodically poor appetite. Otherwise the patient has felt well following the operation. No hemorrhagic tendency. Readmitted 20—10—47: tall for age, thin, normal coloring. Slight enlargement of the liver on the x-ray picture. No ascites. Sedimentation rate 9 mm. Evald's light meal test revealed nothing abnormal. Hgb. 13.6 g%; R.B.C. 4.32 mill.; W.B.C. 13 200; thrombocytes 296 000. Diff.: stabs 11; segmented 37; eosinophils 10; lymphocytes 37; monocytes 5. Icterus index 1: 8. Hijman v.d. Bergh dir. neg., indir. trace. Takata neg. Thymol test 3 units. Serum cholesterol 181 mg%, albumin 3.7 %, globulin 4.4 %, A/G 0.8. Hemolytic resistance: 0.38—0.28 % NaCl.

*Case 5.* M. 186—44. Girl b. 17—2—37. Several cases of diabetes mellitus among relatives. Patient previously healthy. Acute hepatitis July 43; recovered in Oct. same year, when icterus index 1: 8. Jan. 44 cold with fever, thereafter tired, with tendency to epistaxis. Glycosuria was established and the patient admitted to the hospital Feb. 44

(Medical Department, K.L.C.H.). Ordinary development. Somewhat thin and pale, slightly icteric. Liver and spleen not palpable. The latter appeared somewhat enlarged on the x-ray picture. No ascites. Temp. subfebrile. Sedimentation rate 47 mm. Tuberculin test neg. Hgb. 13.0 g%; R.B.C. 4.40 mill.; W.B.C. 7200; thrombocytes 130 000. Diff.: nothing noteworthy. Prothrombin time 26 sec. Hemolytic resistance: 0.46—0.44 % NaCl. Icterus index 1: 15. Hijman v.d. Bergh dir.  $\div$ , indir. +. Takata pos. Urine: trace of sugar on one occasion, urobilin +++, bilirubin  $\div$ . Stools: Weber test  $\div$ . Blood sugar normal. Glucose tolerance test: somewhat diabetes-like curve. Galactose test: 4.3 g excreted. Diagnosis: hepatic cirrhosis. — After discharge the patient gradually improved. June 45 admitted for check-up. Spleen still not palpable but the x-ray picture showed it to be larger than previously. The liver not enlarged. Sedimentation rate 9 mm. Hgb. 12.7 g%; R.B.C. 4.28 mill.; W.B.C. 4800. Diff.: normal. Prothrombin time 21 sec. Icterus index 1: 10. Hijman v.d. Bergh dir.  $\div$ , indir. +++ Takata pos. Galactose test: 2.9 g. excreted. — Thereafter the patient felt well but suffered occasionally from epistaxis. Check-up examination 9—2—48: tall for age, rather thin. Colour normal. Spleen considerably enlarged, liver normal in size. No ascites. X-ray of esophagus: no varices. Sedimentation rate 4 mm. Wassermann neg. Hgb. 11.5 g%; R.B.C. 3.98 mill.; W.B.C. 3600; thrombocytes 94 000; reticulocytes 6 %. Diff.: slight relative lymphocytosis. Sternal puncture (Nordenson): marrow rich in cells, without specific features. Prothrombin time 17 sec. Bleeding and clotting times normal. Hemolytic resistance: 0.38—0.34 % NaCl. Icterus index 1: 7. Hijman v.d. Bergh dir.  $\div$ ; indir. trace. Takata neg. Galactose test: 1.6 g excreted. Thymol test 1 unit. Serum cholesterol 184 mg%, of which 93 mg% ester bound. Phosphatase 21 units. Urine: urobilin and bilirubin  $\div$ . Benzidine test on feces neg.

*Case 6.* M. 399—45. Girl b. 21—2—34. Previously healthy. Summer 44 occasional pains in the left part of the abdomen. Feb. 45 rhinitis and subfebrile temperature. Abdominal circumference increased. Mar. 45 admitted to Medical Department, K.L.C.H. Somewhat pale and thin. Considerable enlargement of the spleen. Liver of normal size. No ascites. X-ray of esophagus: no varices. Tuberculin test and Wassermann neg. Temp. subfebrile. Sedimentation rate 38 mm. Hgb. 12.2 g%; R.B.C. 3.83 mill.; W.B.C. 5000; thrombocytes 190 000; reticulocytes 22 %. Diff.: stabs 7.5; segmented 35; eosinophils 1.5; lymphocytes 42; monocytes 14 %. Sternal puncture (Nordenson): marrow rich in cells, without specific features. Icterus index 1: 16. X-ray of heart: moderate enlargement. Eeg. normal. Urine: albumin, sugar, urobilin and bilirubin  $\div$ . Upon discharge afebrile but sedimentation rate still elevated. Diagnosis: splenomegaly. — For the next 2 years the patient was sub-

jectively free of distress. Summer 47 headache and nausea. Examination in Out-patient Department 6—9—47: normally developed with first signs of puberty. Thin, slightly dyspneic. Considerable enlargement of the spleen, possibly ascites. Sedimentation rate 18 mm. Hgb. 11.5 g%; R.B.C. 3.82 mill.; W.B.C. 1740; thrombocytes 206 000. Diff.: nothing worthy of note. Icterus index 1: 32. Urine: urobilin + + +. 15—10—47 acute deterioration with fever, vomiting, and diarrhea. Admitted following day: affected, lethargic, icteric, slightly cyanotic. Widened vein net in the abdominal wall. Ascites. X-ray: spleen increased in size since preceding examination, liver shadow not delimitable. Sedimentation rate: 14 mm. Hgb. 11.2 g%; R.B.C. 3.58 mill.; W.B.C. 7600; thrombocytes 108 000; reticulocytes 22 %. Diff.: immature 2; stabs 27; segmented 51; lymphocytes 12; monocytes 8 %. Prothrombin time 58 sec. Icterus index 1: 44. Hijman v.d. Bergh dir. and indir. + + +. Takata pos. Thymol test 19 units. Hemolytic resistance: 0.38—0.24 % NaCl. N.P.N. 24 mg%. Urine: albumin  $\frac{1}{2}$ , urobilin +, bilirubin + +. After repeated hematemesis the patient died in hepatic coma 19—10—47. Autopsy (Lindberg): 300 ml cloudy exudate in abdomen. Spleen much enlarged (1200 g) with firm consistency and brownish-red cut surface. Liver typically cirrhotic in appearance (880 g.). Considerable esophageal varices. No thrombosis in the portal vessels. Microscopic examination of the spleen: no follicles, distinct fibroadenia in some places in the pulp. Diagnosis: hepatic cirrhosis + pneumonia + peritonitis.

*Case 7.* M. 450—48. Girl b. 19-1-35. Healthy previously except for chickenpox, measles, and mumps. Jaundice April 43; under care at Borås Hospital with diagnosis acute hepatitis (hepatitis cirrhosis). Liver still enlarged when patient was discharged. — Thereafter subjectively well. Summer 47 first signs of fatigue. Jan. 48 jaundice again. Readmitted to Borås Hospital. Pale, thin, with infantile physical development and dirty yellow skin colour. Petechiae in the face. Liver palpable, with firm margin just under the arcus. Spleen considerably enlarged, almost to the level of the umbilicus. No ascites. Sedimentation rate 92 mm. Hgb. 9.3 g%; R.B.C. 3.1 mill.; W.B.C. 5100. Diff.: normal. Sternal puncture (Nordenson): specimen rich in cells, without specific characteristics. Bleeding and clotting times normal. Hemolytic resistance: 0.42—0.28 % NaCl. Hijman v.d. Bergh dir. +, indir. 3.4 mg%. Takata pos. Serum cholesterol 90 mg%. Thymol test 18 units. Urine: urobilin + + +, bilirubin  $\frac{1}{2}$ . Diagnosis: splenomegaly. — April 48 admitted to Medical Department, K.L.C.H. Very thin, almost cachectic. Upon palpation the spleen in particular but also the liver proved to be enlarged; on the x-ray picture, however, the liver appeared to be of normal size. No ascites. No esophageal varices. X-ray of heart and lungs normal. Tuberculin test and Wassermann negative. Temp. afebrile.

Sedimentation rate 55 mm. Hgb. 9.6 g%; R.B.C. 2.70 mill.; W.B.C. 3700; thrombocytes 98 000; reticulocytes 17 %. Diff.: stabs 6.5; segmented 45.5; eosinophils 1.5; basophils 0.5; lymphocytes 34.5; monocytes 11.5 %. Bleeding and clotting times normal. Prothrombin time 16 sec. Hemolytic resistance: 0.42—0.24 % NaCl. Sternal puncture (Nordenson) as before, specimen rich in cells, without specific characteristics. Icterus index 1: 40. Hijman v.d. Bergh dir. +, indir. ++. Takata pos. Thymol test 23 units. Serum albumin 1.95, globulin 5.10 %, A/G 0.4. N.P.N. 35 mg%. Urine: alb., sugar-, urobilin + + +, bilirubin—. Diagnosis: hepatic cirrhosis.

*Case 8.* M. 678—20. Girl b. 4-1-18. Previously healthy except for measles. Dec. 20 sudden hematemesis. Admitted to Medical Department K.L.C.H. Delicate build, thin, quite pale with cutaneous hemorrhages here and there. Spleen distinctly enlarged. Liver not palpable. No ascites. Tuberculin test neg. Hgb. 10.6 g%; R.B.C. 4.34 mill.; W.B.C. 14 200; thrombocytes 82 500. Bleeding time 5 min., coagulation time 15 min. Stools: Weber test pos. Diagnosis: purpura. — After a 2 yr. interval free of symptoms renewed hematemesis in Dec. 22 and thereafter repeated gastroesophageal hemorrhages. On one occasion transitory ascites. Anti-syphilitic treatment was attempted in spite of the negative Wassermann but without result. July 25 splenectomy, Maria Hospital (Key): liver macroscopically normal. Spleen rather firm, easily removed. — Renewed hematemesis only one month after operation. Subsequently repeated hemorrhages at intervals of a few months up to a few years. 1926 transitory ascites following a hemorrhage. 1943—46 injection treatments of varices in esophagus (Frenckner); no lasting effect. Aug. 47 Talmá's operation (Brandberg): following extirpation of the spleen the omentum was very adherent; only a moderately large flap of the omentum could be made available for sewing in. — After the operation the hemorrhages continued. Takata neg. on repeated occasions. Sedimentation rate normal. Diagnosis: Banti's syndrome.

*Case 9.* M. 203—36.<sup>1</sup> Boy b. 24-7-34. At the age of 6 months pharyngitis with gastroenteritis; otherwise healthy. Feb. 36 sudden hematemesis. Admitted to Medical Department, K.L.C.H. Hgb. 6.5 g%; R.B.C. 3.5 mill.; W.B.C. 7800. Liver and spleen palpable a good finger's breadth below the areus. Diagnosis: secondary anemia. Nov. 38 readmitted because of anemia. Thin, very pale. Liver and spleen not palpable. Wassermann and tuberculin test neg. Hgb. 6.0 g%; R.B.C. 3.7 mill.; W.B.C. 8200; thrombocytes 203 000. Diff.: stabs 3; segmented 32; eosinophils 8; lymphocytes 55; monocytes 2 %. Stools: Weber test negative. Sedimentation rate 17 mm. Sternal puncture (Nordenson):

<sup>1</sup> Case published previously by K. Kaijser in Nord. Med. 6: 978, 1940 (Swedish).

specimen rich in cells with preponderance of the erythropoiesis. While in the hospital hematemesis and melena. Bleeding and clotting times normal. Rectoscopy: varicose hemorrhoidal plexus. X-ray: considerable enlargement of the spleen, esophageal varices. Esophagoscopy (Frenckner): no demonstrable varices (only the upper part of the esophagus could be inspected). Icterus index 1: 8. Hijman v.d. Bergh dir. and indir.  $\frac{1}{2}$ . Takata neg. Galactose test: no excretion. Responded only slightly to anti-anemic treatment. Diagnosis: stenosis of the splenic vein. — 21-3-39 splenectomy (Hindmarsh): liver of normal size, consistency, and colour. Spleen strikingly large and firm (140 g); some adhesions to the colon. No signs of thrombosis of the splenic vessels. Microscopic examination of the spleen (Henschen): increased trabeculae, large follicles, pulp sclerotic throughout; at one point in a middle-sized vein a small occluding thrombus. — Following operation the patient was without symptoms for 2 years. June 41 renewed hematemesis. X-ray of esophagus: varices unchanged. — Hereafter admitted repeatedly to Medical Department because of anemia secondary to manifest or occult hemorrhages. During the whole period distinct vein net in the abdominal wall. On one occasion ascites in connection with an attack of hematemesis. Takata sometimes pos., sometimes neg. Serum phosphatase on one occasion 24 units. Albumin/globulin in serum 1.0. Serum cholesterol 208 mg%, 75 mg% of which ester bound. Thymol test 1 unit. Hemolytic resistance: 0.44—0.24 % NaCl. Normal number of leukocytes and thrombocytes. Icterus index normal. No urobilinuria.

*Case 10.* K. 294—44. Boy b. 20-5-42. 30—5 hospitalized for septic pharyngitis. 11—6 enlargement of the spleen established. Later good general condition except for slight hypochromic anemia. 30-1-44 sudden hematemesis in connection with pertussis (?). 15—2 ascites. Admitted to Surgical Department, K.L.C.H. Very pale, with markedly protruding abdomen; no details palpable because of ascites. X-ray: enlargement of the spleen and esophageal varices. Tuberculin test neg. Hgb. 9.5 g%; R.B.C. 3.12 mill.; W.B.C. 10 400; thrombocytes 235 000. Diff.: stabs 3.5; segmented 47.5; eosinophils 8; lymphocytes 34; monocytes 7 %. Prothrombin time 16 sec. Bleeding and clotting times normal. Wassermann neg. Sternal puncture (Nordenson): specimen rich in cells, without specific characteristics. Sedimentation rate 20 mm. Takata neg. Stools: Weber test neg. Urine: 0 alb. Diagnosis: stenosis of the splenic vein. 3-3-44 splenectomy (Hindmarsh): moderate ascites. Liver of normal size and appearance. Spleen considerably enlarged (135 g), firm. Microscopic examination of the spleen (Bergstrand): large Malpighian bodies, increase in connective tissue, general hyperemia. No signs of thrombosis. — Postoperative course uncomplicated. 2 years passed without symptoms. Thereafter new hemorrhages 3—4 times a year.

to the Medical Department for check-up. Good general condition. Esophageal varices unchanged. Hgb. 11.3 g%; R.B.C. 3.82 mill.; W.B.C. 8700; thrombocytes 172 000. Hemolytic resistance: 0.30—0.20 % NaCl. Icterus index 1: 12. Hijman v.d. Bergh dir., indir. trace. Takata neg. Serum cholesterin 269 mg%, 158 mg% of which ester bound, albumin 4.6, globulin 3.9 %, A/G 1.2. Thymol test 3 units. — New hematemesis Dec. 47 in connection with fracture of the clavicle. Continued to bleed after admission to the hospital, received c. 15 transfusions in all. After hemorrhages fever and ascites as before. 10-3-48 new operation (Sandblom): anastomosis between the coronary vein and the inferior vena cava. »An increased amount of clear, colourless fluid in the abdomen. Liver of normal size with normal colour and surface. The portal vein was dissected free beginning at the hepatoduodenal ligament; it had undergone pathological change with some sclerosed portions and small protrusions between. The pressure in the portal vein seemed to be very low and the changes continued in a peripheral direction, where the chief obstruction was evidently located. Hence there was little or nothing to be gained by an Eck fistula. The right coronary vein was dilated and taut; at its confluence with the splenic vein the tissues were markedly edematous and the impression was received that there was an inflammatory process underway, possibly thrombosis. No improvement in the patient's condition could be hoped for without an outflow for the coronary vein. Hence the lowest part of the latter was dissected free, divided contiguous to the splenic vein, and anastomosed termino-laterally to the inferior vena cava. Some pulling was necessary to make the anastomosis but it seemed to function well.» Postoperative course good. After a symptom-free interval of a half year there was melena again in Sept. 48. The esophageal varices remain unchanged.

*Case 12.* M. 1107—44. Boy b. 14-8-36, 5 weeks before term. Normal development. Previously healthy except for right inguinal hernia operated on in 1940 and 1943 without complications. Suddenly in April 44 hematemesis and melena in connection with measles. Treated at home for 3 weeks under the diagnosis ulcer of the stomach. Another attack of hematemesis Nov. 44 in connection with smallpox vaccination. Now admitted to K.L.C.H. Pale. Considerable enlargement of the spleen. Wassermann and tuberculin test neg. Sedimentation rate 12 mm. Hgb. 9.3 g%; R.B.C. 3.62 mill.; W.B.C. 8000; thrombocytes 30 000. Diff.: immature 5; stabs 22; segmented 29; lymphocytes 39; monocytes 5 %. Prothrombin time 24 sec. Bleeding and coagulation times normal. Hemolytic resistance: 0.42—0.34 % NaCl. Sternal puncture (Nordenson): relatively poor in cells, morphology virtually normal. Icterus index 1: 5. Hijman v.d. Bergh dir., indir. trace. Takata neg. Galactose test: 1.1 g excreted. X-ray of esophagus: no definite varices. Urine: 0 albumin, sed. normal, urobilin ++, bilirubin ÷. Stools: Weber

*Case 11.* M. 979—44. Girl b. 15-4-43. At the age of 17 mo. admitted to Medical Department, K.L.C.H., for paresis in the legs (following poliomyelitis? — no cerebrospinal fluid changes). Incidental findings: enlargement of the liver and especially of the spleen and thrombocytopenia of 20 000—180 000. No microscopic hematuria. Bleeding and coagulation times normal. Prothrombin time 23 sec. Sedimentation rate 18 mm. Hgb. c. 10.0 g%; R.B.C. c. 4.0 mill.; W.B.C. 3500 to 12 000. Diff.: normal. Tibia puncture (Nordenson): virtually normal conditions. Tuberculin test and Wassermann neg. Diagnosis: essential thrombocytopenia. — After discharge the patient was subjectively well. March 47 sudden hematemesis. Readmitted Medical Department. Pale, considerable enlargement of the spleen. X-ray: esophageal varices. Sedimentation rate 15 mm. Hgb. 7.5 g%; R.B.C. 2.7 mill.; W.B.C. 16 200; thrombocytes 160 000. Diff.: immature 2.5; stabs 5.5; segmented 46.5; eosinophils 5.5; basophils 1; lymphocytes 24.5; monocytes 10.5; plasma-cytes 4 %. Sternal puncture (Nordenson): megakaryocyte damage. Prothrombin time 19 sec. Icterus index 1: 11. Hijman v.d. Bergh dir. and indir. neg. Takata pos. Serum cholesterol 108 mg%, of which 66 mg% ester bound, albumin 3.8, globulin 1.4 %. A/G 2.7. Thymol test 3 units. Urine: 0 alb., 0 sugar, normal sed., urobilin +, bilirubin ±. During stay in hospital repeated gastroesophageal hemorrhages. A persistent rise in temp. was interpreted as resorption fever. Ascites set in. In connection with hemorrhages noticeable variations in size of spleen. In spite of repeated blood transfusions and other anti-anemic treatment steadily declining blood values to c. 3.5 g% hgb. and 1.2 mill. R.B.C. Leukocytes varied between 4600 and 1400, thrombocytes between 52 000 and 160 000. — With the patient in a critical condition and under the diagnosis obstruction in the portal circulation an operation was made 12-5-47 (Sandblom): splenectomy + left nephrectomy + portacaval anastomosis according to Blakemore. «Veins around the spleen rather considerably widened. C. 300—400 ml clear yellow ascites fluid. No macroscopic liver changes. Spleen as large as 2 fists. Upon exposure of the left renal vein it appeared that a pair of veins as wide as knitting needles ran from the ventricle region down to the renal vein; i. e., there was already an anastomosis of the type contemplated. After removal of the kidney the splenic vein anastomosed to the middle branch of the renal vein according to Blakemore. Since the splenic vein could not be mobilized more than 3 cm the anastomosis to the renal vein formed an angle of about 100°, a circumstance which undoubtedly involved a greater risk of thrombosis there.» Microscopic examination of the spleen (Bergstrand): thickening of the sinus walls and an increase in the connective tissue in the parenchyma; pathological picture as in chronic stasis. — Postoperative course surprisingly good in view of the patient's poor general condition before operation. Oct. 47 readmitted

test + + + . Diagnosis: thrombosis of the splenic vein. 7-12-44 splenectomy (Hindmarsh): «liver of normal appearance and size. No ascites. Spleen as large as 2 fists with smooth surface and rather firm consistency, in hilus joined firmly to pancreas tail. No thrombi demonstrable in vessels of spleen hilus, but up above a distinct varicosity with wide, sinuous veins.» Weight of spleen 400 g. Microscopic examination (Bergstrand): marked sclerosis with increase in the width of the trabeculae and thickening of the sinus walls. — Postoperative course without complications. Only 3 weeks after the operation and thereafter several times more, most recently in May 45, renewed hematemesis, always in connection with febrile conditions such as varicellae, otitis, and the like. X-ray of the esophagus now showed distinct varices. The past 3 years completely free of symptoms. Readmitted Feb. 48 for check-up: normal development, rather tall for age with slight obesity and hypogenitalism. No enlargement of the liver. X-ray of the esophagus: still varices. Sedimentation rate: 4 mm. Hgb. 12.2 g%; R.B.C. 4.0 mill.; W.B.C. 9600; thrombocytes 278 000; reticulocytes 3 %. Diff.: stabs 6.5; segmented 44.5; eosinophils 2.5; basophils 0.5; lymphocytes 41.5; monocytes 5 %. Prothrombin time 18 sec. Hemolytic resistance: 0.36—0.32 % NaCl. Bleeding and coagulation times normal. Sternal puncture (Nordenson): specimen rich in cells, normal morphology. Icterus index 1: 10. Hijman v.d. Bergh dir. and indir. neg. Takata neg. Thymol test 12 units.

*Case 13. M. 1133—44. Girl b. 5-8-39.* At age of 1 month at K.L.C.H. for pelvic osteitis. In connection herewith spleen and liver enlargement. Low thrombocyte count, otherwise normal blood picture. Tuberculin test and Wassermann neg. — Check-up in Sept. 41: size of spleen unchanged. Still thrombocytopenia, c. 50 000; otherwise normal blood values. Sternal puncture (Nordenson): specimen poor in cells, normal morphology. Diagnosis: thrombosis of the splenic vein. Virtually free of distress until May 44, when there was an attack of hematemesis. After a further hemorrhage in July 44 readmitted to Medical Department. X-ray: esophageal varices. Hgb. 10.2 g%; R.B.C. 3.5 mill.; W.B.C. 8000; thrombocytes 26 700. 20-10-44 splenectomy (Hindmarsh): «liver normal or only slightly enlarged. Normal passage in the portal vessels.» Microscopic examination of the spleen: thickening of the capsule, sclerotic parenchyma, large, non-sclerotic Malpighian bodies, no thrombosis. — Postoperative course normal. New melena 3 weeks after splenectomy, thereafter free of symptoms for c. 1 year. Subsequently further hemorrhages. Esophagoscopy (Skoog) in Nov. 45 showed numerous small varices in the lower 2/3 of the esophagus. It was felt that injection treatment was contraindicated. Nov. 47 readmitted because of severe hematemesis: pale, thin, but otherwise normally developed. No enlargement of the liver. X-ray: probable increase in the number of

varices in the esophagus. Sedimentation rate 11 mm. Hgb. 7.5 g%; R.B.C. 2.70 mill.; W.B.C. 7200; thrombocytes 196 000; reticulocytes 21 %. Diff.: stabs 3; segmented 40; eosinophils 3; basophils 1; lymphocytes 40.5; monocytes 4 %. Prothrombin time 15 sec. Bleeding and clotting times normal. Hemolytic resistance: 0.36—0.22 % NaCl. Sternal puncture (Nordenson): markedly reactive changes, nothing specific. Icterus index 1: 6. Hijman v.d. Bergh dir. and indir.—. Takata neg. Thymol test 4 units. — 16-1-48 new operation (Sandblom): termino-lateral portacaval anastomosis. »The veins on the lesser curvature of the ventricle much dilated. Hepatogastric ligament indurated and calloused with a large number of small, fragile, sinuous vessels. This condition made the operation extremely difficult. The wall of the portal vein was calloused and thickened between protruding thinner portions. Most probably there was a thrombus in the portal vein. After puncture blood spurted out of the stab to a height estimated at approximately 8 cm. Macroscopically the liver appeared normal. Because of the fragile wall and a number of fragile tributaries only about 2 cm of the portal vein could be dissected free. The vena cava was exposed between the renal veins and the lower liver surface and a Pott's clamp applied. Thereafter the portal vein was divided. It was found to have 3 lumina, 2 of which contained fresh thrombi. These were removed, the separating walls were divided a few mm upwards, and a termino-lateral anastomosis according to Blalock was made.» — The postoperative course was normal the first days but thereafter there was increasing icterus and acholic feces, wherefore it seemed probable that the common bile duct had been ligated in the course of the operation. A cholecystostomy was called for. Later there were signs of cholangitis but gradually the patient became free of symptoms, though only for 2 months. Since then several hemorrhages in the form of melena.

*Case 14.* M. 941—47. Boy b. 28-6-43. When he was 14 days old an erysipelas-like infection of the right foot was treated with a sulfonamide. The abdomen had been prominent as long as the parents could remember. Hematemesis in connection with measles but without preceding symptoms Dec. 45. Admitted to Children's Clinic in Oslo, where enlargement of the spleen and ascites were established. X-ray: esophageal varices. Takata neg. Serum albumin 3.69, globulin 2.71, A/G 1.13. 15-2-46 splenectomy (Surgical Department B). »No ascites. No widened veins in the mesocolon, mesentery, greater curvature, or cardiae portion of the stomach. The liver was of ordinary size and appearance. The splenic vein was of ordinary dimensions. No signs of splenic vein thrombosis or thrombosis of other veins. Moderate widening of the vein on the lower side of the diaphragm in the vicinity of the cardia, likewise moderate widening of several veins in the hepatoduodenal ligament, but no thickening or signs of portal thrombosis. Spleen considerably en-

larged, of normal appearance. No adhesions. Weight 130 g.<sup>s</sup> Microscopic examination of the spleen: fibrosis. — Postoperative course normal. Apart from melena 3 weeks after splenectomy the patient was free of symptoms for 8 months. Thereafter repeated hemorrhages. Sept. 47 admitted to Medical Department, K.L.C.H. Normal development, somewhat thin and pale. Liver not enlarged. No ascites. X-ray: pronounced esophageal varices. Wassermann and tuberculin test neg. Sedimentation rate: 43 mm. Hgb. 11.3 g%; R.B.C. 3.80 mil.; W.B.C. 8400; thrombocytes 340 000; reticulocytes 11 %. Diff.: stabs 1; segmented 23; eosinophils 5; basophils 1; lymphocytes 56; monocytes 7; plasmacytes 7 %. Sternal puncture (Roland-Franzén): specimen rich in cells, variegated lymphatic reaction. Prothrombin time 21 sec. Hemolytic resistance: 0.32—0.18 % NaCl. Icterus index 1: 8. Hijman v.d. dir.—, indir +. Takata neg. Serum albumin 3.3; globulin 4.8 %. A/G 0.7. Thymol test 8.6 units. Urine: 0 alb., 0 sugar, urobilin trace, bilirubin neg. Benzidine test on feces neg. — 1-10-47 new operation (Sandblom): anastomosis between the splenic vein and the renal vein following left nephrectomy, according to Blakemore. «Incision in the old cicatrix. Many adhesions set free. The coronary vein was filled with blood. On the site of its confluence with the splenic vein there was a firm yellow edema up towards the porta. Probably there was a thrombus between the portal vein and the confluence with the coronary vein. No dilatation of the veins on the left side of the colon or the uppermost part of the small intestine. The only possibility of a relieving operation seemed to be through the ligated splenic vein, which was open up to the pancreas tail. When this vein was mobilized a small vein began to bleed excessively, showing that the pressure in the splenic vein was very high. The left kidney was extirpated after division of the vessels adjoining the hilus and the renal vein was led up behind the pancreas. The splenic vein was reinforced with great difficulty with the smallest Blakemore tube inasmuch as the wall was fibrous, and the end was introduced into one tributary of the renal vein and joined to it in the usual way. After the anastomosis the renal vein was bent at a sharp angle and it was not possible to ascertain whether it functioned or not. The results of the operation appeared dubious. — The postoperative course was free of complications. Only 3 months later there were fresh hemorrhages, however, and the patient was readmitted for a further operation. 8-7-48 exploratory laparotomy (Sandblom): «The coronary vein appeared in the beginning to be about the width of a lead pencil and sufficiently dilated for anastomosis with the vena cava, but as it was being dissected free it contracted to the width of a knitting needle only. It was now undoubtedly too narrow to permit a functioning anastomosis. One did not get the impression that there was any venous stasis in the ventricle. The portal vein was then examined; its wall was sclerotic and

the pressure seemed to be very low. Thus there was no reason to make an Eck fistula. The liver was entirely normal in appearance but felt unusually firm. Biopsy of the liver (Bergstrand): chronic hepatitis and stasis in the portal system. — Postoperative course uneventful.

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FROM THE PEDIATRIC CLINIC OF KAROLINSKA INSTITUTET AT KRON-  
PRINSESSAN LOVISA'S CHILDREN'S HOSPITAL, STOCKHOLM  
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## Air Conditioning in Children's Hospitals

by

**GUSTAF BIRCH-LINDGREN, architect, and A. LICHTENSTEIN**

One of the most important considerations in planning children's hospitals is the prevention of cross-infection as far as possible. Investigations carried out in 1935 at Kronprinsessan Lovisa's Children's Hospital in Stockholm have shown that for the period 1926—1933 the average stay in the hospital for a normal case was 29.5 days, but that this time was lengthened to 52.2 days if the patient contracted some new infection in the hospital in addition to his original disease. This was the case with about 30 % of the patients.

Even when the average stay at this hospital has been shortened considerably, as in more recent years, the relative figures remain about the same. It must be borne in mind that apart from the risk to the patient resulting from the contraction of a new disease, there is also an economic aspect to be considered, since it will cost at least twice as much to cure the patient. This may also be expressed by saying that if cross-infection can be prevented, a smaller number of beds can handle the same number of patients.

When planning children's hospitals there are two means of cross-infection to consider: through direct contact — including infections through droplets sprayed by coughing, sneezing, or speech — and indirectly through the air and dust. The latter kind seems to have been largely overlooked earlier, and efforts have been directed chiefly towards measures for preventing direct cross-infection.

To control the air- and dust-borne infections it is necessary

to prevent air from moving from one patient to another. Obviously this can be done effectively if patients are separated from each other by means of airtight walls—that is to say, if each patient is isolated in a single room with separate ventilation. This is the ideal arrangement from this point of view. Careful studies in many quarters have shown that air-borne cross-infections can be avoided if the children are separated from one another in closed rooms or cubicles, which is a handier and space-saving arrangement.

Great efforts have been made to control the cross-infection by other means than by isolation. Floors, bedclothes and the clothes of the patients have been treated with special adherent substances in order to prevent dust from diffusing into the air. Germicidal vapours and ultra-violet rays have been tried. To a certain degree these methods have given promising results, but probably they can never take the place of individual isolation and at the moment can be considered only as a complementary form of protection against cross-infection.

There are psychological drawbacks to individual isolation, especially for older children, and it must first be considered for the care of prematurely born and other infants. The older the children, the less the risks connected with the general cross-infection. That children with infections must be prevented through isolation from spreading disease goes without saying.

In construction of a hospital with a great number of single rooms or with cubicles, the question arises of the heating and ventilation of these units, as the doors of the rooms or cubicles can obviously not be made absolutely airtight, and the air must be prevented from passing from one cubicle to another.

This is possible only if the air is forced into the cubicles, by some mechanical means, and exhausted into the corridor outside. The air pressure must be kept somewhat higher in the cubicles than in the corridor, thus forcing the air to flow from the cubicle under the door or through a vent in the wall into the corridor. At the same time it is necessary that the walls between the cubicles be absolutely tight. It is also of importance to arrange the air-intake high up under the ceiling in order to get

the air flow directed downwards, thus helping to keep the dust down to the floor.

A further condition that is important from a medical point of view is that the temperature be subject to control, and the younger the child the more important this is. At the same time it is very desirable that the humidity also be subject to control, particularly in the cubicles for premature babies. It is not necessary to have separate air conditioning in each cubicle. It would suffice if it were possible to vary the temperature and humidity in each group of 3—4 cubicles forming part of a ward unit for, say, 20 or 26 babies.

The regulation of the pressure, temperature, and relative humidity of the conditioned air constitutes a delicate technical problem, particularly where economy must be considered, involving in many cases the employment of a single central station plant. The air from this plant must be led to each separate cubicle. For the prematures there can be provided either a separate unit for each group or a secondary plant, reheating and rehumidifying the air from the main plant to a higher temperature and humidity.

The return of the used air, or part of this air, to the air conditioning plant and its re-use in order to save heat is common practice where a high degree of sterility of the air is not required, but it presents fundamental difficulties when sterility is essential. Sterilization of the air may be effected by the use of ultra-violet light, but as this creates ozone to such a degree that it may have an intoxicating effect on the children and as no other really reliable way seems to exist, the used air must be exhausted directly into open through ducts designed to carry the exhaust air to the top of the building. These must be separated from one another in such way as to prevent any possibility of contamination of one exhaust duct by another, should the plant by some mishap stop operating.

It will be appreciated that should the plant stop, there is always the possibility of air flowing back through the exhaust duct system with the hazard of contamination unless the precautions outlined are taken. Also, the supply air must be taken

from a place that is remote from any contamination by the exhaust air. An airtight damper should be placed in the main supply duct which would close automatically in the event that the supply fan stopped. This would prevent the air from flowing backwards, which could involve risk of cross-infection.

There are various systems of air conditioning which are suitable for the conditioning of hospitals and it is difficult to determine the best one without careful study of the problems involved. However, in the case of the children's hospitals under consideration in which it is proposed to incorporate a number of small rooms or cubicles, the most suitable system seems to be that of employing a central station air conditioning plant together with air distributing ducts.

The method generally used is to take in fresh air from a place where it is as clean as possible — in general, as high as possible above the ground —, let it pass through a filter and wash it. In the washing process, the air is at the same time humidified to 100 per cent and given the same temperature as the water. After this process the air is heated and led to the rooms to be conditioned. It is clear that there are two ways of controlling the temperature and humidity of the air: (1) during the washing process by regulating the temperature of the water and (2) by the degree of heating to which the air is subjected after the washing process.

It is a known physical law that the amount of moisture air can contain in the form of water vapour is dependent on the temperature of the air. The higher the temperature, the higher the possible moisture content — and vice versa. When the temperature of the water in the humidifier is raised the temperature of the air passing through is also raised and the air will emerge saturated at this temperature — saturated because it is in intimate contact with a finely atomized spray of washing water.

If the air is subsequently raised to a temperature still higher by means of after-heaters, but kept out of contact with water, it will be able to contain more water than would be the case at the lower temperature, and its relative humidity will therefore fall. From this it will be appreciated that the temperature and humidity

of conditioned air can be controlled to any degree of temperature and relative humidity desired. If it is desired to raise the relative humidity in a room, this may be done in two ways:

1. by raising the temperature of the water, in which case the room temperature would be kept constant, or
2. by lowering the temperature of the room, in which case the temperature of the water spray would be kept constant.

In the event that it is desired to raise both temperature and relative humidity, the temperature of the air must be raised to the required degree and at the same time the temperature of the water spray must also be raised sufficiently to ensure that the air contains sufficient water vapour to give the desired relative humidity at this new temperature. The saturated temperature of the air is known as the «dewpoint».

Any combination of temperature and relative humidity is possible by varying the «dewpoint» and «final temperature» of the air.

It should be mentioned here that there are other ways of varying the dewpoint than by varying the temperature of the spray water. It may also be done by mixing return air and fresh air from outside, thus controlling the temperature of the air entering the washer. However, since it is not recommended that any return air be used, this method of varying the dewpoint does not enter into this discussion.

The employment of dewpoint control at the washer and temperature control by means of a single after-heater gives poor flexibility of control in the individual spaces or cubicles to be conditioned. Some supplementary form of heating must be provided in the spaces proper. It will be appreciated that as the sun travels around a building, the part on which the sun's rays fall will require less heating than the parts in the shade. This supplementary heating can be provided by radiators which are thermostatically controlled, and these radiators can be installed in each of the cubicles. In effect, the air supply will provide the necessary ventilating increment together with the proper control of humidity conditions in conjunction with the

thermostatically controlled radiators. Fine control of individual space conditions cannot be obtained without some such arrangement. By ensuring that the temperature never rises too high in any of the rooms, a saving in heat, and therefore in fuel, results — an important matter from the standpoint of economy of operation.

In many places it is necessary to cool and de-humidify the air during the summer months. This changes nothing in the principles involved; it is merely a question of cooling the water in the washer instead of heating it. A refrigerator replaces the boiler; alternatively, if there is a sufficient quantity of well water at a low enough temperature, this may be used in place of a refrigerator.

If the costs of air conditioning can be kept within reasonable limits, then it is desirable that it be extended to other rooms and departments in a children's hospital. The fact to be remembered is that the older the child, the fewer are the risks attached to the commonest cross-infections.

Air conditioning has now come to be regarded as a necessity in hospitals throughout the world and is without question one of the most important ways of ensuring the control of air-borne diseases and the prevention of cross-infections. With careful attention from any ordinarily intelligent and conscientious plant attendant, it will function without trouble indefinitely. Occasional visits from a local service man will ensure that control instruments are kept in proper adjustment.

### **Summary**

The authors emphasize the necessity of considering indirect cross-infection through the air and dust and combating cross-infection by individual isolation in single rooms or cubicles. It is recommended to ventilate and heat these units by employing a central station air conditioning plant together with air distributing ducts. Air pressure, temperature and relative humidity must be controlled. The principles for such an installation are discussed.

### Zusammenfassung

Die Autoren weisen auf die Notwendigkeit hin, die indirekte nosocomiale Infektion durch Luft und Staub zu beachten und zu bekämpfen durch individuelle Isolierung in Einzelräumen oder Boxen. Es wird empfohlen, diese durch Anwendung einer Centralstation als Luftversorgungsanlage mit Verteilungsrohren zu lüften und zu heizen.

### Résumé

L'auteur insiste sur la nécessité de prendre en considération les infections nosocomiales indirectes causées par l'air et la poussière et de combattre ces infections par l'isolation individuelle en chambre ou cabinet privés. Il est recommandé d'aérer et de chauffer ces pièces au moyen d'un appareil central de chauffage et de ventilation avec des tuyaux distributeurs d'air. La pression atmosphérique, la température et l'humidité relative doivent être contrôlées. Les principes d'une telle installation sont discutés.

### Resumen

Los autores recalcan la necesidad de tomar en consideración la infección cruzada indirecta por aire y polvo, y de combatirla por medio de aislamiento individual en piezas aisladas. Se recomienda ventilar y calentar estos cuartos usando una estación central con una instalación de aire acondicionado en combinación con conductos distribuidores de aire. Es necesario controlar la presión del aire, la temperatura y la humedad relativa. Se discuten los principios de una instalación de esta clase.

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## An Attempt to Eradicate Repeated Bacterial Infections in a Family

by

A. LICHTENSTEIN and G. MELIN

Cross infections in children's homes and day nurseries and the methods of combatting these infections are attracting much attention at the present time. In the United States, HAMBURGER's examinations of military personnel and school children have shown that certain streptococcus carriers, particularly those with streptococci in the nose, may also have an abundance of bacteria on their hands, clothes, handkerchiefs, and bed linen; and that even in the vicinity of these carriers, for example in the dust on the floor and in the air, the presence of numerous bacteria can be established. Infection bearers of this type are known as »dangerous carriers». If one such person becomes part of some collective living arrangement such as a military barracks, the result is frequently an explosive outbreak of tonsillitis and other streptococcal infections.

Probably the »dangerous carriers» transmit infection primarily through direct contact or droplet infection conveyed by coughing, sneezing, or close conversation. In certain cases, however, infection is probably also spread via the infected air or dust.

In Sweden studies of »dangerous carriers» have been carried out by LAURELL, LÖFSTRÖM, MELIN, OUCHTERLONY, and WALLMARK. On the whole they have been able to confirm Hamburger's conclusions and in addition they have shown that the same conditions apply to pneumococci (LÖFSTRÖM, MELIN), staphylococci (MELIN, WALLMARK), and diphtheria bacteria (OUCHTERLONY) as to streptococci.

Even in larger families the pediatrician not infrequently encounters series of bacterial infections in the form of tonsillitis, bronchitis, pneumonia, otitis, purulent skin affections, and the like. Now and then familial infections of this type are found which are so stubborn and severe that they constitute a serious threat to the health and working capacity of the members of the family. In one such family we have undertaken a program of «disinfection» (in this sense, freeing both patients and environment of infection) in accordance with the same principles which are applied in the combating of nosocomial infections in child-care institutions.

The family consisted of husband, wife, three children aged 6, 4, and 1, and a nursemaid. They lived in a modern co-operative apartment house. Their apartment included one large and three small rooms with a total floor surface of 90—100 sq. m.

The disease history with which we are concerned here began with the 6 year old. In February, 1947, she had pneumonia in connection with measles and in March erythema nodosum. At that time she reacted negatively to a tuberculin test. Beta-hemolytic streptococci could be cultured from the throat. Upon admission to the hospital the anti-streptolysin titer was 1 600; a week later it was 3 200. During the following months one throat infection succeeded another, while in between the patient was sub-febrile, fatigued, and in generally poor health, so that she could not be said to be really well from March to October.

In the middle of March the mother became ill with a lingering bronchitis and in April the 4 year old sister followed suit with tonsillitis accompanied by high fever. In June all the children had a period of coughing. In connection therewith the mother contracted a severe case of pneumonia from which she did not recover until the end of July. During this month as well as during August, the mother, the nurse, and two of the children had anginal conditions. In September the father and mother had pharyngitis with fever; the 6 year old, tonsillitis; and the 1 year old a rather large cutaneous abscess in the groin. At the end of September and beginning of October all members of the family except the father had tonsillitis and pharyngitis with fever and were in generally poor health.

	February	March	April	May	June	July	August	September	October	November
Mother								Pneumonia		Runn. ing Nose
Father									Phar. A. S. 90	
Daughter, 6 years	Morb. + Pneum. <sup>+</sup> Er. Nod.	Ton.	Ton.	Bronchitis	Ton. A. S. 3 200	Ton.	Ton.		A. S. 1 400	Runn. ing Nose
Daughter, 4 years			Ton.	Bronch.				Ton. A. S. 180		
Daughter, 1 years				Bronchitis				Abscess A. S. 32	Phar. A. S. 250	
Nurse							Ton.		Ton. A. S. 250	

Fig. 1.

The fact that from the beginning of March till the beginning of October there was never a time at which all the members of the family were well at once illustrates their difficult situation (see Diagram, Fig. 1).

With matters in this state, a bacteriological examination of the family with a view to possible eradication of the foci was decided upon. The circumstance that the 6 year old had had hemolytic streptococci in the throat from the beginning and had scarcely been well since that time lent support to the assumption that it was she who was spreading streptococci in the family.

Bacteriological samples from the throat, nose, hands, and clothes were taken from each member of the family. In addition samples of dust were taken. An attempt to examine the bacteria content of the air as well by the use of so-called sedimentation plates came to nothing when the children evinced too much interest in touching them. The samples were collected in the usual way with a swab which was subsequently taken to the State Bacteriological Laboratory in a tube containing serum agar broth. Samples were taken from the hands and clothes with a swab dipped in broth and brushed over the volar and dorsal surfaces of the hands and over the clothes on the part of the body corresponding to the lapels of a coat.

The bacteriological analysis was made by culture on ordinary blood agar containing gentian violet (concentration 1/750 000), which is a good selective substrate for streptococci, and following Chapman's method on agar plates containing phenol and mannitol with a view to ascertaining whether there were any pathogenic staphylococci aurei. In addition mice were inoculated for the isolation of pneumococci. The types of streptococci and pneumococci were determined. Phage typing of the staphylococcus aureus strains which appeared on the plates was also carried out.

Fig. 2 gives a summary of the results of the bacteriological examinations.

The first sample was taken on Sept. 10. None of the members of the family was acutely ill at that time, but both parents and the 4 year old had recovered about a week before from a pharyn-

Mother	10.9 βTNHC	17.9 βSH	5.10 —	6.10 Pn6TNHC	7.10 —	8.10 —	9.10 —	10.10 —	11.11 —	15.1 —
Father	— —	— —	— —	— —	— —	— —	— —	— —	— —	— —
Daughter I	— —	— βSRC	— Pn6TNHC	Staph. T Pn6TNHC	Staph. T Pn6TNHC	Pn6TNHC Pn6TNHC	Pn6TNHC Pn6TNHC	Pn6TNHC Pn6TNHC	Pn6TNHC Pn6TNHC	— —
Daughter II	βST —	— —	— —	— —	— —	— —	— —	— —	— —	Pn6H —
Daughter III	βST —	— βST	— —	— —	— —	— —	— —	— —	— —	— —
Nurse	βST —	— —	— —	— —	— —	— —	— —	— —	— —	— —
Floor Dust	— —	— $\beta_8 \left\{ \begin{matrix} cb \\ pb \\ sr \\ nr \end{matrix} \right.$	— Pn6Hi	— Pn6Hi	— Pn6Hi	— Pn6Hi	— Pn6Hi	— Pn6Hi	— Pn6Hi	— —

T = throat  
N = nose  
H = hands

C = clothes  
pb = parents' bedroom  
cb = children's bedroom

sr = living room  
nr = nurse's room  
Hi = hospital isolation room

Fig. 2.

geal infection. The mother proved to have streptococci in both throat and nose and on her hands and clothes, and thus could probably be regarded as a carrier in Hamburger's sense. Unfortunately determination of the type of these streptococci was unsuccessful. The 4 year old, 1 year old, and nurse had beta-streptococci, type 8, in the throat.

The second test was taken on Sept. 17, when all the children and the nurse had a pharyngeal infection. On this occasion beta-streptococci, type 8, were found in the respiratory passages of two of the children and on the mother's hands. In addition many streptococci of the same type were found in the dust from the floor.

For more than half a year the 6 year old had suffered almost continuously from infections, and as in October she seemed to be fatigued and listless, she was admitted to Kronprinsessan Lovisa's Children's Hospital for observation. A thorough examination of the circulatory organs, kidneys, ears, nose, and throat revealed nothing abnormal, however. Bacteriological samples were taken every day and although no beta-streptococci were found in the patient's respiratory tracts, numerous type 6 pneumococci were found both in the throat and nose and on the hands and clothes. On a few occasions staphylococci aurei were found but apparently they had not been of any epidemiological significance. The strains which were found did not react to phages and therefore the type could not be determined.

On October 10 new samples were taken from all the members of the family at home except the father in connection with the inauguration of penicillin treatment. On this occasion the somewhat surprising discovery was made that all those examined had type 6 pneumococci. The mother proved to be the carrier. Cultures from both the nurse and the dust on the floor showed streptococci and type 6 pneumococci.

It can scarcely be doubted that in the first place the beta-hemolytic streptococci played an important part in the infections in the family. The 6 year old's repeated tonsillitis with continuously high anti-streptolysin titer month after month would seem to indicate that her infections, at any rate, were

primarily of streptococcal character. In addition, on several different occasions the presence of streptococci of the same type was established in all the other members of the family except the father. In conjunction with an acute throat infection in all the children and the nurse the presence of quantities of streptococci was established in floor dust from different parts of the apartment.

One wonders, however, whether other pathogenic micro-organisms may not have played a certain etiological rôle. It may be that the absence of high anti-streptolysin values in the other members of the family indicates this, even though they too had had repeated throat infections. The appearance of type 6 pneumococci at the close of the examination period, immediately after the entire family with the exception of the father had had tonsillitis with fever; the circumstance that several members of the family were spreaders of pneumococci; and the further circumstance that in connection with the appearance of pneumococci the streptococci disappeared from most of the samples may speak in favour of a pneumococcal origin for certain of the family's later infections. Unfortunately antibody examinations in connection with these yielded no definite results.

Finally, certain of the family members' lighter cases of pharyngitis without fever may have been virus-conditioned.

Thus there are strong reasons to suspect that in the first place type 8 beta streptococci and possibly in the second, type 6 pneumococci caused the family's infections. As far as the infection-spreading mechanism goes, the clinical course would seem to indicate that the 6 year old was the primary source of contagion in the family.

There is also reason to assume that the floor dust and possibly even the air operated as sources of contamination. The extraordinarily large collection of streptococci in the dust suggests that it must have been highly infectious.

Under these circumstances an attempt at sterilization seemed to be indicated. The first object was to render any carriers harmless, and the second to prevent by means of thorough cleaning of the apartment a later secondary infection via the infected dust.

Since both the streptococci and the pneumococci had proved to be sensitive to penicillin and the streptococci resistant to sulfa, we carried out penicillin treatment of the whole family except the father, who had on the whole been well and whose samples had never shown either streptococci or pneumococci. The penicillin was given in the form of penicillin solution in oil and beeswax (Abbott) in a dose of 300 000 units for the adults; 150 000 for both the older children; and 75 000 units for the 1 year old per day for 8 days. Thereafter the family had to leave the apartment while it underwent a thorough cleaning. The floors, panelling, and window sills were washed with chloramine solution. The air in the rooms was treated with the aerosol »Aeryl II».

Upon a later bacteriological check-up of the family and the apartment neither streptococci nor pneumococci could be found.

During the year which has since elapsed the family has enjoyed remarkably good health. There have been no more serious cases of infectious disease but only a few slight head colds without any fever worthy of mention and without effect on the general condition of the persons concerned. It seems evident to us that the sterilization program undertaken broke off the earlier 8-month long succession of infections in the family. The mother said, »We haven't been so well for years».

Hence the results would appear to encourage similar attempts to cure stubborn and severe bacterial family infections.

#### Summary

In a family consisting of six persons, three of whom were children aged 1—6, all except the father had continual infections of the respiratory tract, sometimes with high fever, during the period March—Oct. 1947. Bacteriological examination revealed that all except the father were carriers of beta-streptococci which in all except one were of type 8. Some had typical beta-streptococci even on their hands and clothes. The floor dust also proved to contain an abundance of type 8 streptococci, a circumstance which indicates the presence of one or more so-called »dangerous carriers». Several had increased anti-streptolysin titers. A further sampling a few weeks later in connection with a new family

epidemic of throat infections showed considerably fewer streptococci but abundant type 6 pneumococci in three persons, all of whom were dangerous carriers. Bacteria were also found in the dust on the floor.

All members of the family except the father were treated for a week with penicillin, after which the apartment was thoroughly cleaned. Among other things the floors and panelling were washed with chloramine solution and the air was treated with »Aeryl II».

Since this disinfection both of the family and their home the chain of family infections seems to have been broken. Only brief, slight, upper respiratory tract infections with long intervals between have appeared.

#### Résumé

Dans une famille de 6 personnes dont trois enfants de 1—6 ans, tous, sauf le père de famille, avaient souffert d'infections des voies respiratoires, dans la période mars—octobre 1947 et même d'une forte fièvre. Un examen bactériologique a montré que tous, sauf le père de famille, étaient porteurs de  $\beta$ -streptocoques, lesquels chez tous, un excepté, pouvaient se classer dans le type 8. Chez quelques-uns on a aussi constaté le même type  $\beta$ -streptocoque sur les mains et sur les vêtements. La poussière du plancher contenait aussi grand nombre de streptocoques type 8. Cela indique la présence d'un, ou de plusieurs de ce qu'on appelle: porteurs dangereux. Plusieurs membres avaient un titre d'antistreptolysin élevé. Une nouvelle prise d'épreuve, deux ou trois semaines plus tard, au moment d'une épidémie dans la famille d'infections dans la gorge, a montré un nombre considérablement moindre de streptocoques mais par contre, une abondance de pneumocoques type 6 chez trois membres, lesquels étaient tous transmetteurs d'infection. On a trouvé aussi des bactéries dans la poussière du plancher.

Tous les membres de la famille, sauf le père de famille, ont été traités par la pénicilline durant une semaine, après quoi l'appartement a été soigneusement désinfecté—c'est-à-dire: le plancher et les boiseries lavés à la chloramine et l'air traité par »Aeryl II».

Après la désinfection la chaîne des infections répétées dans la famille semble rompue. Seules, de courtes et légères infections des voies respiratoires ont été constatées à longs intervalles.

#### Zusammenfassung

In einer 6köpfigen Familie, darunter 3 Kinder im Alter von 1—6 Jahren, hatten von März bis Oktober alle ausser dem Familienvater wiederholte Infektionen der Luftwege, ab und zu mit hohem Fieber. Die bakteriologische Untersuchung ergab, dass sämtliche ausser dem Vater Träger von  $\beta$ -hämolsierenden Streptokokken waren, welche bei allen mit Ausnahme eines als zum Typus 8 gehörig bestimmt werden konnten. Bei einigen fand man typengleiche  $\beta$ -Streptokokken auch an Händen und Kleidern, auch der Fussbodenstaub enthielt zahlreiche Typus 8  $\beta$ -Streptokokken. Dies spricht für das Vorhandensein eines oder mehrerer sog. gefährlicher Träger. Mehrere Familienmitglieder hatten erhöhten Antistreptolysintiter. Eine neue ein paar Wochen später im Anschlusse an eine neuerliche Familienepidemie einer Racheninfektion vorgenommene Untersuchung zeigte einen bedeutend geringeren Befund an Streptokokken, dagegen reichlich Penumokokken vom Typus 6 bei 3 Mitgliedern, die alle Bacillenstreuer waren. Die Bakterien wurden auch im Bodenstaub vorgefunden.

Sämtliche Mitglieder, ausser dem Vater wurden eine Woche lang mit Penicillin behandelt, wonach die Wohnung gründlich gereinigt wurde, was eine Kloraminwäsche des Fussbodens und der Panele und Behandlung der Luft mit »Aeryl II« umfasste.

Nach der Genesung schien die Kette der wiederholten Familieninfektionen unterbrochen zu sein. Nur kurze leichte Infektionen der oberen Luftwege traten mit langen Zwischenräumen auf.

#### Resumen

En una familia de 6 personas, de las cuales tres eran niños entre 1 y 6 años, todos menos el padre habían tenido infecciones continuas en las vías respiratorias, a veces con fiebre alta. Un examen bacteriológico demostró que todos, menos el padre,

eran portadores de estreptococos B que se podían determinar como del tipo 8 en todos los casos menos en uno. En algunos miembros de la familia se encontraron, también en las manos y en los vestidos, cocos de un tipo parecido a los estreptococos. También se vió que el polvo del piso contenía abundantes cantidades de estreptococos del tipo 8. Esto indica la presencia de uno o varios portadores peligrosos. Varios miembros de la familia tenían título aumentado de antiestreptonina. Un nuevo examen que tuvo lugar unas semanas más tarde con motivo de una epidemia familiar de infecciones de la garganta, demostró hallazgos menos abundantes de estreptococos, pero, por el otro lado, gran abundancia de neumococos del tipo 6 en tres de los miembros de la familia, todos los cuales eran diseminadores. También se encontraron bacterias en el polvo del piso.

Durante una semana todos los miembros de la familia, menos el padre, fueron objeto de tratamiento con penicilina, después de lo cual se limpió esmeradamente la casa, incluyendo lavado con cloramina del piso y del entablado y tratamiento del aire con »Aeryl II».

Después del saneamiento parece que la cadena de infecciones continuas en la familia ha sido rota. Sólo ligeras infecciones de corta duración en las vías superiores respiratorias se han presentado con largos intervalos.

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## The Electroencephalogram in Cases of Tuberculous Meningitis

by

A. LICHTENSTEIN and K.-A. MELIN

Formerly the prognosis in cases of tuberculous meningitis was almost hopeless. Nowadays, thanks to streptomycin, treatment is often more successful. Yet many cases still defy treatment, ending either in death or in recovery with more or less serious defects.

Hence determination of the prognosis in individual cases has come into the foreground. It has proved difficult, however. Some cases run a malignant course from the beginning in spite of intensive treatment. Others show themselves somewhat responsive to treatment, but pass into a subchronic stage characterized by hydrocephalus, pareses, convulsions, and deterioration of the intellect. Still others respond to treatment well in the beginning but later suffer relapse. Finally, in certain cases treatment gives excellent results, i. e. complete or virtually complete restoration to physical and psychical health.

We attempt to determine the prognosis and individualize treatment by utilizing all available control methods. The cerebrospinal fluid is examined directly for tubercle bacilli and used in cultures and guinea-pig tests. The cell content and albumen content of the C.S.F. are determined continuously, as well as the lumbar sugar-blood sugar quotient. The Goldsol reaction also seems to be of value, as are the streptomycin concentration in the blood and the lumbar fluid. Continuous checking of the eyegrounds for chorioidal tubercles and papillary stasis are

also important in ascertaining the course of the disease, and frequent checkings of vestibular and cochlear function are a matter of routine.

Yet in spite of all these examinations it is often very difficult to determine the prognosis in any one case. Therefore information concerning the actual condition of the cerebral cortex is of great value. Earlier investigations (ROSS 1945, GIBBS and GIBBS 1947, PACELLA and ASSOCIATES 1947, HOLMGREN 1948) have shown that acute meningo-encephalitic processes are reflected in the electroencephalogram. Hence we have felt it of interest to follow our cases of tuberculous meningitis electroencephalographically, particularly in view of the possibility of thus obtaining further aid in the determination of the prognosis.

In the beginning some doubt was cast on this possibility by the investigations of JOHNSON and ASSOCIATES (1946) into the influence of antibiotics on the central nervous system. By means of experiments on animals these investigators showed that penicillin, streptomycin, streptothricin, and other antibiotics have a distinct effect on the EEG. If antibiotics in varying concentrations were applied to the exposed cerebral cortices of cats and monkeys, the occurrence of spikes, in particular, but also of isolated slow waves could be noted on the EEG. In this respect the effects of penicillin appeared to be more pronounced than those of streptomycin.

Therefore we examined first 2 children aged 2 months and 8 months. They were treated with streptomycin for miliary pulmonary tuberculosis without meningitis or other signs of cerebral affection. At the time of the examination the streptomycin concentration in these children's blood varied between 5 W.E. and 15 W.E. The electroencephalograms recorded showed no pathological changes. Thus no electroencephalographically recordable cerebral effects could be demonstrated in these patients, who upon being treated with streptomycin showed ordinary concentrations in the blood.

Under these circumstances it seemed possible to us that electroencephalographic control of our tuberculous meningitis cases might give valuable results.

As yet our investigations include only a few cases, but we have decided to make a preliminary report on the results in order to stimulate similar investigations in other places where a large body of meningitis material is available. All our examinations were made at the electroencephalographic laboratory at Kronprinsessan Lovisa's Children's Hospital with a Grass electroencephalograph, Model III. Silver disc electrodes stuck to the scalp with collodion were used. Between the electrodes and the scalp there was a thin layer of electrode jelly. A total of 10 electrodes were applied in each examination, namely, frontally, parietally, temporally, and occipitally on both sides, in addition to which the ear lobes were used as «indifferent» electrodes. Both unipolar and bipolar recordings were made from all the electrodes.

Thus far 7 children aged  $1\frac{1}{2}$ —11 years have been examined. All have had bacteriologically verified tuberculous meningitis and have undergone streptomycin treatment. All 4 cases which were examined early in the course of the disease then showed pathological changes on the electroencephalogram.

After completed streptomycin treatment 2 of the children, a 6 year old boy and a 3 year old boy, were clinically completely cured. After clinical recovery they were again examined electroencephalographically, in the first case 5 and 10 months after the onset of the disease and in the second 7 and 15 months afterwards. The EEGs of both children were interpreted as normal, although somewhat generally slow in the case of the 6 year old.

The first EEG examination, c.  $3\frac{1}{2}$  months after the onset of the disease, of a 2 year old girl who showed considerable clinical improvement during treatment revealed bursts of large 5/sec. waves on the record (Fig. 1). Shortly after this phenomenon was observed there was clinical deterioration, and a second EEG examination c.  $2\frac{1}{2}$  months later showed marked pathological changes. Approximately 1 month thereafter the child died and autopsy revealed an abundance of tubercles in the gray matter of the brain. In this case the EEG was the first examination method to indicate that the disease was becoming worse.

An 11 year old boy was examined only once, c. 4 months

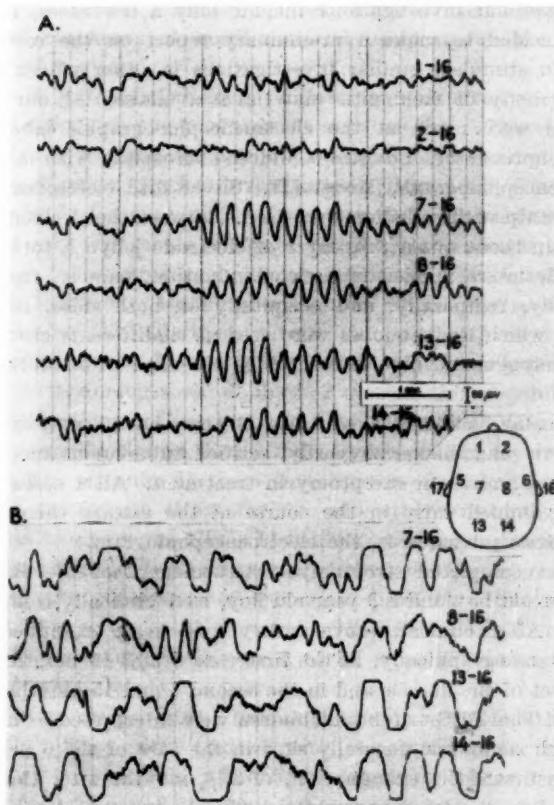


Fig. 1. 2 year old girl. A.  $3\frac{1}{2}$  months after onset of disease.  
B.  $2\frac{1}{2}$  months later.

after the onset of meningitis (Fig. 2.). Bursts of enlarged 4/sec. waves were noted on the record. This patient, who died 4 months later, also proved to have an abundance of tubercles in the gray matter.

In the other 3 cases EEG examinations were carried out repeatedly. A  $1\frac{1}{2}$  year old girl and a  $4\frac{1}{2}$  year old boy both

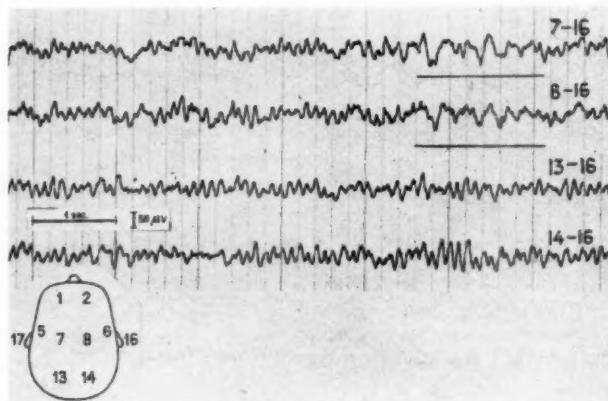


Fig. 2. 11 year old boy 4 months after onset of disease. Bursts of enlarged 4/sec. waves on EEG.

showed considerable clinical improvement. At the first EEG examination 11 days (Fig. 3.) and 3 days, respectively, after the onset of the disease, both showed a generally and pronouncedly pathological EEG with many large, slow waves. The EEG in both gradually became normal, and at the present time, 12 and 7 months, respectively, after the onset of the disease, is fully normal. It is noteworthy that this normalization process took place in the course of intensive intramuscular and intratethal streptomycin treatment. This lends further support to our assumption that the EEG changes produced by antibiotics in experiments do not arise in clinical treatment, at any rate not to such an extent that they are able to affect appraisement of the actual condition.

In the seventh case, a  $2\frac{1}{2}$  year old girl, the first EEG examination was made 3 months after meningitis was established. At the time her clinical condition was good and the record was entirely normal. This was still the case when she was examined a month later. About 3 weeks thereafter clinical symptoms of deterioration appeared, with a rise in temperature, bad humour, general indisposition, and vomiting. The lumbar fluid showed an

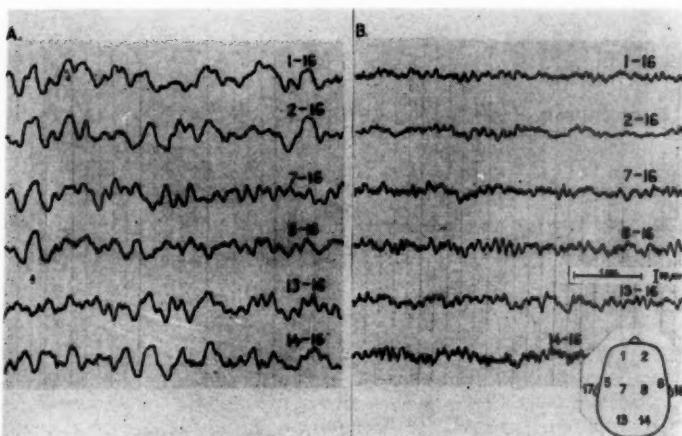


Fig. 3.  $1\frac{1}{2}$  year old girl. A. 11 days after onset of disease. B. 5 months later.

increase in the number of cells, increasing albumen content, and somewhat less lumbar sugar than before. At the same time repeated EEG examinations revealed bursts of large 5/sec. waves (Fig. 4).

Of the 7 patients examined at Kronprinsessan Lovisa's Children's Hospital, 4 have recovered or shown considerable clinical improvement thus far. All of these have also had a normal EEG. Of the other 3 patients, 2 have died and 1 has shown symptoms of clinical deterioration. As their conditions have deteriorated the electroencephalograms of these 3 have shown bursts of 4—5/sec. waves of high amplitude. In one of the cases such EEG findings constituted the first indication that the patient was becoming worse. Thus to judge by these investigations, repeated EEG checkings throughout streptomycin treatment of tuberculous meningitis definitely help the examiner to follow the course of the disease. The EEG may even provide the first observable indication of deterioration and thus be of prognostic value. If the EEG becomes more pathological in the course of treatment, it may also indicate the desirability of intensifying the treatment.

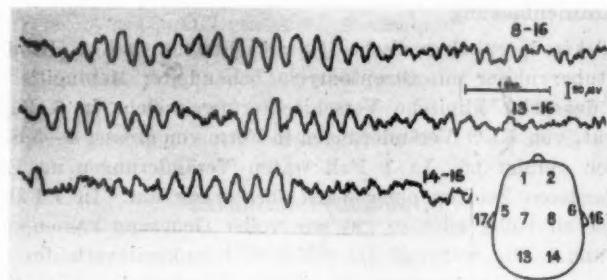


Fig. 4. 2  $\frac{1}{2}$  year old girl 4  $\frac{1}{2}$  months after onset of disease. Clinical symptoms of relapse accompanied by bursts of enlarged 5/sec. waves on EEG.

### Summary

Electroencephalographic examinations of 7 children with streptomycin-treated tuberculous meningitis showed that clinical deterioration, which set in in 3 cases, was accompanied by EEG changes in the form of large 4—5/sec. waves. In 1 case EEG changes were the first indication of deterioration. In 4 cases which were restored to complete or almost complete health the EEG changes noted earlier in the disease disappeared. Thus repeated EEG recordings may be of prognostic value and even indicate a need for intensified treatment.

### Résumé

Les examens encéphalographiques de 7 enfants ayant méningite tuberculeuse traitée par la streptomycine, montrent que l'aggravation clinique constatée dans 3 cas est accompagnée de changements EEG sous forme de grandes ondes 4—5 sec. Dans 1 cas les changements EEG étaient les premières indications de l'aggravation. Dans 4 cas, lesquels ont entièrement ou presque entièrement recouvré la santé, les changements EEG, survenus auparavant au cours de la maladie, ont disparu. Des contrôles EEG répétés peuvent donc avoir une valeur pronostique et peuvent aussi indiquer la nécessité d'intensifier le traitement.

### Zusammenfassung

Elektroenzephalografische Untersuchungen bei 7 Kindern mit tuberkulöser mit Streptomycin behandelter Meningitis zeigen, dass eine klinische Verschlechterung, welche in 3 Fällen auftrat, von EEG Veränderungen in Form von grosser 4—5/Sek.-Wellen gefolgt ist. In 1 Fall traten Veränderungen im EEG vor anderen Zeichen einer Verschlechterung auf. In 4 Fällen, welche zu voller oder so gut wie voller Genesung kamen, verschwanden die während des früheren Krankheitsverlaufes aufgetretenen Veränderungen des EEG. Wiederholte EEG Kontrollen können deshalb von prognostischem Wert sein und auch die Notwendigkeit einer intensiven Behandlung stützen.

### Resumen

Los exámenes electroencefalográficos en niños de 7 años con meningitis tuberculosa tratada con estreptomicina muestran que una deterioración clínica, que comenzó en 3 casos, fué acompañada de alteraciones EEG en forma de grandes ondas de 4—5 segundos. En un caso las alteraciones EEG fueron la primera indicación de deterioración. En cuatro casos, que han sido completa o casi completamente curados, las alteraciones EEG, observadas al principio de la enfermedad, han desaparecido. Repetidos controles EEG pueden ser de valor para el pronóstico y pueden indicar la necesidad de un tratamiento intensificado.

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## **Essential Fructosuria**

### **Report of a Case**

by

**BIRGER BROMAN, M. D.**

Essential fructosuria or, as it is also called, essential laevulosuria is an extremely uncommon metabolic disturbance of an altogether harmless nature. It is characterized by the inability of the body to make full utilization of fructose whether this is administered in a non-complex form as a monosaccharide in fruit and honey or as a disaccharide in cane or beet sugar. The disturbance is manifest as the presence of fructose in the urine in a certain proportion to the amount of sugar of this kind administered. The urine therefore proves reducing and the true nature of the disorder can be overlooked or possibly misinterpreted as diabetes mellitus. It can therefore be of practical interest.

In January 1943 an 8-year-old girl was treated for fructosuria at Kronprinsessan Lovisa's Hospital for Children in Stockholm. The case-history was briefly the following: The patient had earlier been healthy on the whole and had developed normally. No diabetes mellitus nor other metabolic diseases in the family. The parents and a 10-year-old brother were healthy. At Christmas 1942 the child became ill with an acute upper respiratory tract infection and high fever. Sulphathiazole was prescribed and the patient was given altogether 10 tablets (= 5 g) during a few days. The temperature fell rapidly and she became afebrile after three days. In connexion with the infection and chemotherapy a urine test was made as a matter of routine and gave a positive

Almén reaction. A control test one week later gave the same result and the patient was therefore admitted to hospital with the diagnosis of glycosuria. The mother then stated that she thought that the patient had lost weight although her appetite was good, but no marked thirst nor large volumes of urine had been observed.

Examination revealed nothing remarkable. The patient was somewhat thin but her general condition was good. Height 135 cm, weight 27.3 kg. During the first three days the urine showed a reducing capacity corresponding to 2—8 g of glucose per 24 hours. No acetonuria was present. A 24-hour curve for the blood sugar and a glucose tolerance test with 1 g of glucose per kg of body weight gave entirely normal values. A closer chemical analysis of the sugar species in the urine was performed and showed that the reducing substance consisted entirely of fructose. (The urine proved to reduce a quantity corresponding to 0.46 per cent of fructose and to be laevorotatory 0.54° corresponding to 0.49 per cent of fructose. In addition, the urine fermented with baker's yeast and after fermentation was no longer reducing nor optically active. Seliwanoff's reaction was strongly positive in a manner entirely typical of fructose.<sup>1)</sup>

Further investigations were directed to a study of the patient's sugar metabolism under various conditions and the following results proved to be of interest.

A double glucose tolerance test gave entirely normal results and showed a positive Staub-Traugott effect, i. e. no appreciable elevation in the blood-sugar level after a second dose of glucose in contradistinction to the conditions in diabetes mellitus.

Administration of insulin had not the slightest effect on the patient's daily excretion of sugar in the urine (v. diagram).

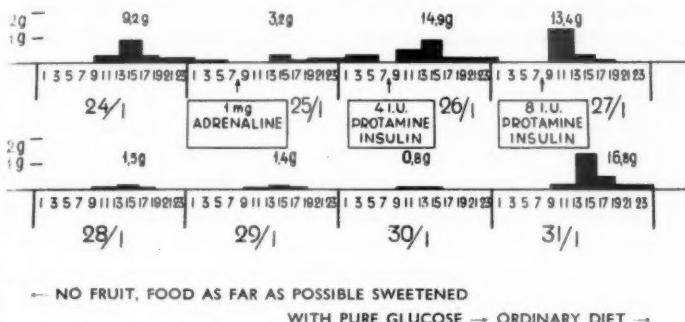
Adrenaline tests with 1 mg of the substance subcutaneously resulted in a normal elevation of the blood-sugar picture and no increase in fructosuria (v. diagram).

Fructose deprivation by means of the exclusion of fruit from the diet and as far as possible replacing the ordinary sugar with

<sup>1</sup> I wish to express my thanks to Dr. B. Josephson for performing these tests.

the same quantity of pure glucose was the only way in which it was possible to decrease the fructosuria despite the administration of sugars (v. diagram).

#### 8 DAYS' EXCRETION OF SUGAR IN THE URINE OF THE PATIENT



*Laevulose tolerance tests* which in normal individuals usually cause no excretion of sugar in the urine or any marked fructosuria gave rise to both in our patient. After administration by mouth of 29 g of laevulose, the patient excreted 4 g (= 13.8 per cent) in the urine within four hours and no appreciable elevation of the blood sugar occurred. A patient with fresh diabetes and no insulin treatment underwent a laevulose tolerance test at the same time. In this case there was a considerable elevation of the blood sugar similar to that with a glucose tolerance test, no fructosuria but glycosuria.

A follow-up examination of the patient in December 1948, nearly six years after hospitalization, showed that she still suffered from fructosuria. Her development was normal, height 170 cm, weight 56.1 kg.

How can the disturbance in metabolism present in this case be explained? The fructose level in the blood is affected by the following three factors: 1) the rate of resorption, 2) the rate at which fructose is converted into glucose or glycogen and 3) the rate at which the fructose is oxidized or is converted into fats.

It is considered that it is particularly when the liver is unable to remove fructose from the blood as rapidly as it is resorbed that the unconverted sugar is found in the blood and fructosuria occurs. It is the liver that converts the fructose into glucose and especially, stores the fructose in the form of glycogen. Owing to the prime importance of the liver for the metabolism of fructose, it has been considered that a deficient function of this organ is the cause of the anomaly in metabolism present in essential fructosuria.

Some authors state that normally 80—90 per cent of the fructose ingested is converted into glycogen and the remainder broken down into lactic acid. In essential fructosuria this latter fraction would not be broken down but would be excreted unconverted owing to the lack of the enzyme necessary for the purpose.

No complete incapacity for utilizing the fructose thus exists and, fairly constantly, only a certain percentage of the quantity of fructose ingested (usually approximately 13 per cent) is found in the urine.

Fructosuria is extremely uncommon and hitherto — since 1884 when the first case was described — no more than about fifty cases have been reported. All ages and races are represented and in one case the duration was 25 years. It has been calculated that fructosuria occurs in one out of 130 000 individuals, and that this figure is probably on the high side. MARBLE (1946) stated that in a series of 28 000 cases of diabetes mellitus he found only four cases of fructosuria.

From reports of cases published hitherto, three factors appear to indicate that fructosuria is hereditary as a recessive character: 1) fructosuria is common among siblings, 2) fructosuria is not encountered in parents or children of individuals suffering from the disorder, 3) parents of children with fructosuria are often related.

A study of the records of our hospital during a seven-year period revealed that during this time 21 patients had been treated under the diagnosis of benign glycosuria. The case-sheets of these patients were studied thoroughly in order to ascertain whether any further case of fructosuria could be found. It then

transpired that in eight of these cases the species of sugar had already been investigated and was found to be glucose in seven instances. In the eighth case it was probably not a question of glucose, but owing to the minute quantity of the substance in the sample it was impossible to determine the species and subsequent repeated urine tests gave a negative Almén reaction.

Among the thirteen cases in which a chemical analysis had not previously been made, it was found that only three of these children had shown daily excretion of sugar in a manner typical of fructosuria. They then underwent a follow-up examination but only one child had any excretion of sugar in the urine on this occasion and it proved to be glucose. These facts appear to emphasize the accuracy of the opinion that essential fructosuria is a very uncommon metabolic disturbance.

#### Summary

A study is made of the sugar metabolism in an 8-year-old girl suffering from fructosuria.

Neither the administration of adrenalin nor of insulin affected the excretion of sugar in the urine. The only way in which the fructosuria could be decreased despite the administration of sugars was by fructose deprivation, i. e. the exclusion of fruit from the diet and the replacement, as far as possible, of ordinary sugar with the same quantity of pure glucose.

Six years after the first examination the patient shows normal development but the fructosuria is still present.

#### Résumé

Une étude du métabolisme du sucre chez une fillette de 8 ans souffrant de fructosurie.

Ni l'adrénaline, ni l'insuline n'ont empêché l'excrétion du sucre dans l'urine. La seule manière dont la fructosurie puisse être diminuée, malgré l'administration de sucre, était la privation de fructose c-à-d l'exclusion des fruits dans l'alimentation et le remplacement, autant que possible, du sucre ordinaire par la même quantité de glucose pur.

Six ans après le premier examen la patiente montrait un développement normal mais la fructosurie était encore présente.

### Zusammenfassung

Es wurde eine Untersuchung gemacht über den Zuckerumsatz bei einem 8jährigen Mädchen, das an Fruktosurie litt.

Weder die Anwendung von Adrenalin noch Insulin beeinflusste die Zuckerausscheidung im Urin. Der einzige Weg, auf dem die Fruktosurie vermindert werden konnte, trotz Verabreichung von Zucker, war die Entziehung von Fruktose, d. h. das Ausschalten von Obst aus der Diät und der Ersatz, so weit das möglich war, des gewöhnlichen Zuckers durch dieselbe Menge reiner Glykose.

6 Jahre nach der ersten Untersuchung zeigte die Patientin normale Entwicklung, aber die Fruktosurie ist dauernd vorhanden.

### Resumen

Se estudió el metabolismo de azúcar en una muchacha de 8 años que sufre de fructosuria.

Ni la administración de adrenalina ni la de insulina afectaban la excreción de azúcar en la orina. La única manera por la cual se podía disminuir la fructosuria, no obstante la administración de azúcar, fué por medio de la privación fructosa, es decir, la exclusión de fruta en la dieta y su reemplazamiento, en la medida de lo posible, por azúcar corriente con la misma cantidad de glucosa pura.

Seis años después del primer examen el enfermo mostró normal desarrollo, pero la fructosuria persiste todavía.

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FROM THE PEDIATRIC CLINIC OF KAROLINSKA INSTITUTET AT KRON-  
PRINSESSAN LOVISA'S CHILDREN'S HOSPITAL, STOCKHOLM.  
CHIEF: PROFESSOR A. LICHTENSTEIN.

## Ulcerative Colitis in Children<sup>1</sup>

by

RUTGER LAGERCRANTZ

This investigation represents a clinical, prognostic and, to some extent bacteriological study of 134 cases of ulcerative colitis in children.

The *definition* of ulcerative colitis (u. c.) or severe, suppurative colitis, as it was formerly called is *chronic catarrh of the large intestine with bloody, purulent evacuations and unknown etiology*. Thus it does not include cases of severe colitis caused by tuberculosis, bacillary or amebic dysentery, syphilis, venereal lymphogranuloma, tumor or polyposis.

### *Survey of Literature*

The literature on this disease in adults is very extensive. The first Gastro-enterological Congress, held in Brussels in 1935 was partly devoted to u. c. Materials on nearly 1 000 cases has been published in America. Several Scandinavian authors have made a thorough study of the disease. So far SVARTZ and MOLTKE have the largest bodies of Scandinavian material.

The literature relating to u. c. in children is on a far smaller scale. However, in 1923 the American HELMHOLZ wrote the first paper on 5 cases. After that, isolated cases were published so that in 1937 GLANZMANN and ASCH, who wrote the first German-language paper on the disease were able to collect 20 cases from the literature when publishing an account of 2 cases of their own. In 1940 JACKMAN, BARGEN and HELMHOLZ published the

<sup>1</sup> With a grant from Karolinska Institutet, Stockholm.

largest childmaterial so far (95 cases). In some Scandinavian material there is occasional reference to children's cases, but as yet none in Scandinavia has investigated the occurrence of the disease specifically in children.

#### *Etiology, Pathogenesis and Pathological Anatomy*

The *etiology* of u. c. has long been disputed.

Most investigators have considered the disease to be caused by an infection. All bacteria of the intestinal flora have been under suspicion. HURST, among others, held that u. c. was a chronic bacillary dysentery. BARGEN believed that he had found the cause in a specific type of streptococcus. Other investigators have maintained that the enterococci or other intestinal cocci play an important part in the origin of the disease (SVARTZ, GRUMBACH and others). These theories have been subjected to strong criticism, and the problem of the etiology of ulcerative colitis is still unsolved. Other factors may eventually play a part in the etiology. A number of writers have shown interest in their patients' constitutions. Among others, the Swede LINDÖ has found that cases of u. c. frequently have allergic manifestations or cases of allergy in the family. Especially in recent years, the significance of psychological factors has been emphasized (in Sweden by GUNNARSSON).

According to the literature on the subject, the *pathogenesis* and *pathological anatomy* seem to be the same whether the disease attacks children or adults. It arises in the submucosa of the rectum and in most cases spreads along the colon. It is possible that in children the disease shows a greater tendency to attack the ileum as well (HELMHOLZ).

#### *Occurrence and Clinical Features*

The disease seems to be more common, or at any rate is diagnosed more frequently, in America than in Europe. In the Mayo Clinic during the period 1925—1931 one child out of every 274 admitted was found to be suffering from u. c. It is said to be as common among boys as among girls, and to increase in

frequency up to the time when its peak is reached between the ages of 20 and 40.

Using their extensive material, JACKMAN, BARGEN and HELMHOLZ were unable to discover any common predisposing factors. However, the majority of their cases first appeared and tended to relapse at those seasons of the year when infections of the upper respiratory tract are prevalent.

The disease is described as starting in two ways which differ in principle. 1. An insidious beginning: a slightly affected patient has 1—5 semi-solid or solid evacuations containing blood daily. The subsequent development of the disease in these cases is slow. 2. An acute beginning: patients in this group show serious symptoms from the outset: they feel ill and are forced by fever and frequent diarrhea containing blood to go to bed. In these cases the condition often undergoes a rapid change, generally for the worse.

In the large body of American material (e. g. JACKMAN, BARGEN and HELMHOLZ) adult cases are about equally divided between the two groups, whereas the primarily chronic type is most common in the Scandinavian Countries (MOLTKE, SVARTZ). Out of 95 child cases in the material collected by JACKMAN, BARGEN and HELMHOLZ the onset of the disease was acute in 77 %.

The first symptom may be pallor and loss of flesh.

The most important symptom is hemorrhagic, usually loose evacuation of the bowels. If the rectum only is attacked the patient may be constipated, in which case the evacuation is solid with blood on the surface. If major parts of the colon are affected the patient's evacuation is loose. If the ileum is also attacked the patient will have unusually abundant evacuations and a symptomatic picture similar to that of a celiac disease (GLANZMANN and ASCH).

The pain is as a rule not very severe. In the acute stages, however, many patients have severe rectal tenesmus or diffuse abdominal pains unconnected with meals. They soon become fatigued, irritable and thin in spite of having a good appetite during the initial stage. Many slight cases run their course with-

out the patient's becoming feverish. Patients may have ulcers without a temperature or a temperature without ulcers (MOLTKE). The type of fever varies, in the beginning the patients often are subfebrile, while in the final stage the fever may become septic.

According to the literature the patient is usually found upon preliminary examination to be thin and pale. The abdomen is often distended and meteoristic and part of the colon is palpated as a sensitive string. Occasionally eczema, hemorrhoids or condylomata are observed near the anus. Per rectum the sphincter sometimes feels more than normally contracted. Frequently there is blood or mucus on the glove.

According to most authors the blood usually shows hypochromic or sometimes normochromic anemia which is regarded as proportionate to the patient's emaciation and the severity of the disease; the extent of the pathological changes in the colon is said to be of minor significance (POLLARD and associates). The white blood picture exhibits as a rule slight leucocytosis with a shifting to the left. Generally values over 20 000 are found only in the event of complications or the terminal stage (MOLTKE). In cases of long duration leucocytosis is frequently absent. Eosinophilia is considered uncommon. In light cases the sedimentation rate is only slightly elevated. According to MOLTKE and SVARTZ, values over 20 mm/1 hr. indicate deeper ulceration or some complication.

The feces are generally evil-smelling and contain mucus, pus and blood. According to HELMHOLZ, abundant hemorrhage is more common in children than in adults. Microscopical examination seldom reveals signs of poor digestion. The primary changes in the intestinal flora are not clear. When the disease has developed, enterococci or other cocci are found to predominate. Secondary changes in the intestinal flora frequently involve increased putrefaction or carbohydrate fermentation; in the latter case there is often an increased quantity of iodophile clostridia (SVARTZ).

A test breakfast usually shows normal values. HURST, BOAS and others considered that persons suffering from achylia were

predisposed to the disease. In more recent investigations, e.g. MOLTKE's, the number of cases of hypochylia or achylia is set at about 20 %.

The majority of investigators consider that all cases of suspected u. c. should undergo rectoscopic examination. Some pediatricians, on the other hand, hold that diagnosis should be made without subjecting the child to the irritation of rectoscopy. Since the disease almost invariably starts in the rectum, a normal picture argues against the diagnosis u. c. In the early stages the mucous membrane is edematous and reddened and tends to bleed easily. Frequently it is granulated and coated with mucus, pus or tufts of fibrin. In the later stages one may observe ulcers coated with mucus or pus between swollen, granulated islets of mucus-membrane and slightly retracted scars. (Thus it is not necessary to prove ulcers to diagnose u. c.) The changes are generally most pronounced distally.

X-ray examination is essential in order to determine the extent of the disease. If it has attacked the rectum only, the X-ray picture of the colon will be normal. The earliest symptom indicating that the colon has been attacked generally takes the form of rapid emptying of the contrast medium, an abundance of haustra and irregular mucous membrane relief. Subsequently the haustra gradually disappear, and it is sometimes possible with a thin contrast layer to disclose an ulcer. In severe chronic cases the appearance of the colon in the X-ray photograph is typical and has been likened to a lead-pipe, since the haustration is entirely absent and the lumen constricted.

#### *Course of the Disease*

Most acute cases run their course without remissions. However, the disease seldom proves fatal before the patient has been ill for 2 or 3 months. Most of the deaths occur during the first year of the disease, according to ELITZAK and WIDERMAN and MOLTKE.

As a rule, the primary chronic forms show a tendency to remission after only a few months, with or without treatment. When a remission of the disease occurs, the subjective symp-

toms may be slight or absent altogether, yet examination of the feces and rectoscopy frequently reveal signs of u. c. The disease shows a marked tendency to relapse. Often the patient is unable to give any reason for his deterioration in health. In many cases there is deterioration in conjunction with infections of the upper respiratory tract (JACKMAN, BARGEN and HELMHOLZ).

#### *Complications*

Complications are common. JACKMAN, BARGEN and HELMHOLZ found complications in 41 % of their 871 cases. Among the 95 patients who were under 16 years of age when they became ill complications were somewhat more common (47 %). The duration of the disease varied between 3 months and 20 years. Their material also shows that multiple complications are more common in adults than in children.

A distinction is made between complications in or in the vicinity of the intestine and complications in other parts of the body. The most common local complication is *polypi*. Svartz does not regard this as a complication but as a symptom of long-standing severe disease. In large bodies of material the frequency has been about 15 % (HURST, JACKMAN, BARGEN and HELMHOLZ). The second most common local complication is alleged to be *strictures*, which have occurred in about 12 % of the cases. *Cancer* in the colon is often secondary to polyposis. MONES and SANJUAN set the frequency at 2 % and JACKMAN, BARGEN and HELMHOLZ at 3.2 % for their entire material, but 6.3 % for the 95 cases of the disease which appeared before the age of 16 and were observed for periods ranging from 3 months to 20 years (on the other hand, polyposis was more common among the adult cases). Recently SVARTZ has shown a relative high incidence of cancer in her material. *Abscesses* and *fistulae* round the rectum occur in about 8 %. (According to JACKMAN, BARGEN and HELMHOLZ, somewhat more frequently among adults than children.) — *Perforation* of the intestine is uncommon, though HURST gives the frequency as 3 %. It is a late or a terminal complication. Some authors regard it as a complication if the process attacks the ileum. HELMHOLZ has described 2 cases of children with this complication. Both died, and the diagnosis was made at the autopsy.

The most common complication outside the intestine is stated to be *arthritis*. According to HURST (733 cases) it occurs in 4%; according to JACKMAN, BARGEN and HELMHOLZ (871 cases) in about 6%. The latter consider it to be about as common in children as in adults. In the Scandinavian materials it is less common. MOLTKE had only one case of arthritis among his 125 cases. Up to 1941 SVARTZ had not seen a single case. According to MONES and SANJUAN, arthritis is most common in the thumb, shoulder and tibiotalar joints. Generally the patients have similar symptoms in several joints. The first symptoms are swelling, redness and tenderness. The course is chronic, but permanent restrictions of movement are rare. — Other relatively uncommon skeletal complications are osteoporosis (GLANZMANN and ASCH) and drumstick fingers (ELITZAK and WIDERMAN).

Next to arthritis, affections of the skin are the most common complication outside the intestine. JACKMAN, BARGEN and HELMHOLZ reported about 1.5% skin complications in their material. The most common type, or at any rate that which has attracted the most attention, resembles erythema nodosum. In some cases the eruption has been combined with joint symptoms. In all the cases described, Mantoux was negative. — In addition, isolated cases of other dermal complications have been described, such as eczema, erysipelas, purpura and, somewhat more frequently dermal ulcer.

One relatively usual complication is said to be *hypovitaminosis*, which as a rule is secondary to a diet deficient in vitamins.

Other complications are thought to be rare. *Phlebitis* occurs only in isolated cases in the largest materials. Ulcer in the oral cavity and the oesophagus has been described by HELMHOLZ, among others, as a terminal complication in children.

Isolated cases of *injury to the liver* have been described in some of the larger bodies of materials (e. g. BARGENS and CAMFORT, BARGEN & MORLOCKS). In 1947 TUMEN, MONAGHAN and JOBB described 5 cases of hepatic cirrhosis out of 151 cases of u. c. All had had protracted severe u. c. and low serum albumen, and the authors assert that there is a connection between hepatic cirrhosis and the basic disease.

### *Diagnosis and Differential Diagnosis*

As a rule it is easy to diagnose hemorrhagic, purulent colitis on the basis of the anamnesis and the patient's condition. Subsequently it is necessary to exclude known causes. The course of *bacillary dysentery* and the *salmonella infections* is almost invariably acute and usually does not resemble the remittent course and the complications of u. c. In every case of severe colitis, however, it is essential to make repeated bacteriological feces cultures in order to exclude these diseases. *Amebic dysentery* does not occur in northern countries; otherwise it renders differential diagnosis extremely difficult. *Intestinal tuberculosis* is as a rule secondary to far advanced pulmonary tuberculosis. Independent tuberculosis of the colon starts almost without exception in the ileo-cecal tract in contrast to u. c. The course of the disease shows no pronounced remissions and the complications are different. In children particular attention should be paid to the tuberculin tests. *Polyposis* may be a complication following upon u. c. As an isolated phenomenon it occurs especially in children. Such cases have bloody but not purulent feces of normal consistency and the disease follows a course different from that of u. c. It can easily be diagnosed with the aid of rectoscopy and X-ray examination. *Intestinal syphilis*, *terminal ileitis*, *lympho-granulomatosis*, *diverticulitis*, *cancer* and *hemorrhoids* are uncommon in children and, as a rule, may easily be distinguished from u. c.

It is generally easy to make a differential diagnosis between u. c. and *spastic colitis*, *nervous colitis* (Bargen's *irritable colon*) if these cases are followed for a relatively long period with regular feces examinations, rectoscopy and X-ray.

### *Prognosis*

When doctors began to diagnose this disease seventy years ago its prognosis was poor. Gradually, however, they learned to recognize cases earlier when the prognosis was better. The bodies of material they examined were as a rule small, the periods of observation frequently short and the history very often incom-

plete. It is difficult, therefore, to compare different materials. Owing to the marked tendency of the disease to spontaneous remission and relapse, the long-range prognosis must be cautious. JACKMAN, HELMHOLZ and BARGEN considered that a patient had not recovered his health until he had been free of symptoms for at least two years. In 1947 M. PAULSON, of the Johns Hopkins Hospital stated that sooner or later all cases of u. c. suffer relapse.

The rate of mortality in adults is indicated in different materials as from 3 to 26 %. The most common cause of death has been progressive u. c. The number of those entirely free of symptoms is given as between 20 and 76 %. The mortality is higher and the longterm prognosis worse in the United States than in Scandinavia.

In HOLT's textbook on pediatrics it is stated that the prognosis is far better for children than for adults. The opinion generally held has been just the opposite. JACKMAN, BARGEN and HELMHOLZ were able to show that 22 out of 95 children's cases (23 %) died, as opposed to 148 of all their 871 cases (17 %). About the same number of children as adults were actively ill, but the number of children entirely well after at least 2 years was smaller. Out of ELITZAK and WIDERMAN's 23 children's cases, 8 died. 14 of the remainder were under observation for a minimum of  $1\frac{1}{2}$  years and a maximum of 12 years; 5 were then subjectively and objectively healthy, 3 showed improvement and 6 were actively ill. HELMHOLZ has written two articles on a total of 12 children's cases; of these only 2 died, while the rest improved in health. Thus to judge from the literature on the subject, the prognosis would appear if anything to be worse for children than for adults, and the younger the child the worse the prognosis.

However, the manner in which the patient falls ill is regarded as more important than the age at which the disease sets in. An acute initial attack and a course without remissions are considered to be bad signs. Some investigators, e. g. SNAPPER, have believed that the spread of the process in the intestine plays an important part in the prognosis. Others, such as WILLARD,

have shown that the spread seems to be of minor significance. Progressive anemia, a sedimentation rate of over 20 mm/1 hr., and a shifting to the left of the white blood corpuscles over 30 % have been given as signs of a bad prognosis (MOLTKE and others).

#### *Treatment*

Most authors consider that at any rate in the beginning cases of u. c. should be nursed in the hospital. HURST would have the patient remain in bed as long as there are more than two bowel movements per day, while other writers have permitted the patient to get up earlier. Formerly these cases were kept on a strict diet. Nowadays, however, the tendency is to give them sufficient and varied diet but one poor in cellulose. The results of this treatment appear to be more satisfactory. SVARTZ gives these cases a relatively free diet rich in calories and excluding only the coarser vegetables. She considers that a diet containing an excessive amount of albumen (like some intestinal diets prescribed for children) may injure the intestine through increase of albumen decomposition (personal communication). Moreover, in the majority of cases extra vitamins should be added to the diet parenterally or by mouth.

Among the methods of causal treatment of u. c., the sulfanilamide drugs are now regarded as of paramount importance. Penicillin and streptomycin have been tried in a number of cases, as a rule without any striking effect. Of the sulfanilamide compounds, the best to administer is said to be a drug which gives a high intestinal concentration but is not much re-absorbed (salazopyrine, phtalylsulfathiazol, sulfaguanidin, sulfadigesine etc.). In 1939 SVARTZ began to treat u. c. with sulfapyridine with good results. She now uses salazopyrine and considers it both superior to and less dangerous than sulfapyridine. She has presented some excellent results in several papers, and in 1946 published 124 cases treated with salazopyrine 75 of which were subjectively healthy and 45 of which showed improvement. The complications arising from the treatment were of relatively little significance. The white blood corpuscle picture and urine should be checked regularly.

In 1941 ÖHNELL described 22 cases of u. c. treated with sulfapyridine, uliron C and sulfathiazole, 20 of which showed improvement. In 1943 HOLST described 9 cases treated with salazopyrine, sulfamethylthiazole and sulfapyridine in 4 of which improvement was attributed to the chemotherapy. In 1941 ELITZAK and WIDERMANN treated 10 children with sulfathiazole or other similar drugs, with relatively poor results. In 1942 STREICHER described 912 cases 109 of which had been treated with sulfanilamide. The results were poor, the best being obtained with sulfathiazole. In 1945 STREICHER was able to show far more favourable results with phthalylsulfathiazole (sulfthalyl), no less than 74 cases out of 80 having improved. Subsequently BARGEN and several other American authors have reported satisfactory results with drugs of a similar type.

Most authors report only on the immediate results. In view of the great tendency of the disease to spontaneous remissions and relapses, however the long term results are of special interest. COLLINS re-examined 39 cases 4—7 years after treatment with sulfadiazine and neoprontosil and found that the late results were not as good as the immediate results.

Some authors have considered that psychical treatment should form part of the causal therapy in u. c. and have reported excellent results (in Scandinavia, GUNNARSSON).

A number of methods of treatment which were formerly considered specific are now regarded as non-specific or else symptomatically active. BARGEN obtained excellent results with his specific serum and vaccine and HURST with large doses of dysenteric serum. Other investigators have not confirmed these results. In a number of cases an improvement has been obtained after inoculation with a vaccine prepared from bacteria (notably enterococci) from the patient's own intestine. ROCHWALSKY considered blood transfusion a specific remedy. Other writers have not obtained such good results with it, though many have improved the patient's general condition and blood values with repeated blood transfusions. Iron is considered indicated in most cases of anemia and patients generally stand it well. When the anemia is normochromic POLLARD recommends blood trans-

fusions instead. Many cases seem to derive benefit from spasmytics (SVARTZ).

Local treatment has long been regarded as important. The question of whether or not to give local treatment has not been as ardently discussed as the form which local treatment should take . . . However, HARDY, BULMER and MOLTKE warn against giving an enema in acute stages. SANJUAN and MONES recommend small enemas with saline solution. SVARTZ recommends enema with 1/8—1 % collargol solution or, in certain cases, lucosil (sulfanilamide compound) in agar-agar. A large number of other solutions and mucous mixtures have also been suggested. When the disease is attended by constipation, a loosening diet and mild laxatives are recommended. In such cases bismuth and calcium, which may be used, may be injurious.

The results of surgical and medical treatment cannot be compared. As a rule, the patient has not been operated on until after a long period of fruitless medical treatment or in the event of a vital indication. Hence the primary mortality is high. In some series, however, an operation was performed early in selected cases. CAVE reports 4 fatal cases out of 50 operated on and good late results among the rest. The best technique is considered to be ileostomy, which in isolated cases it was possible later to close. Operative treatment is far more common in America than in Scandinavia.

### The Writer's Own Investigations

The material consists of 134 cases of u. c. which occurred before the patients reached the age of 15. The medical history records for all of the patients' stay in the hospital (277 records) form the basis of this article.<sup>1</sup> The majority of the cases (76) were treated at the Stockholm Children's Hospital, all cases from 1920 up to the end of May 1948 having been included. Thanks to the courtesy of Professor SVARTZ it has also been possible to include 27 cases treated at Karolinska Sjukhuset. These

<sup>1</sup> The author has worked over the primary material himself. A summary report on the material with diagram (I) is given in table 1.

*Table 1.*  
Summary of all cases.

**Explanations:**

Medical History Record no.:

A.S. = Akademiska Sjukhuset, Uppsala.

Boden = Central Hospital, Boden.

Ersta = Ersta Hospital, Stockholm.  
Sp. = Hospital for infectious diseases, Stockholm.

Falun = Central Hospital, Falun.

Gbg = Children's Hospital of Gothenburg.

Gävle = Central Hospital, Gävle.

Kars. = Central Hospital, Karlstad.  
Krist. = Central Hospital, Kristianstad.

K.L.B = Kronprinsessan Lovisas Children's Hospital, Stockholm.

K.S. = Karolinska Sjukhuset, Stockholm.

L. = University Clinic, Lund.

Lin. = Central Hospital, Linköping.  
Norrk. = Central Hospital, Norrköping.

Norrt. = Norrtulls Children's Hospital, Stockholm.

Sachs. = Sachs' Children's Hospital, Stockholm.

Sam. = Samariten, Children's Hospital, Stockholm.

Ö. = Central Hospital, Örebro.

**Rectoscopy:**

I = reddened, oedematous, easily, bleeding.

II =      \*      \*      \*      \* and granulated.

III =      \*      \*      \*      \* ev. granulated and with ulcers or scars.

**X-ray-examination (spread of disease):**

I = rectum only (normal x-ray of colon).

II = rectum and lower part of colon.

III = rectum and entire colon.

VI = rectum, entire colon and lowest part of ileum.

**Chemotherapy:**

1 = salazopyrine, 2 = salazothiazol, 3 = sulfathiazol, 4 = sulfadimin, 5 = sulfapyridine, 6 = penicillin, 7 = sulftahyl, 8 = sulfaguanidin, 9 = streptomycin, 10 = sulfadital, 11 = elkosin, 12 = sulfadigesin, 13 = prontosil, 14 = agar-lucosil-enema, 15 = lucosil-enema.

**Complications:**

1 = arthritis, 2 = stomatit. aphtos., 3 = perirectal abscess, 4 = anal excema, 5 = prolapse of rectum, 6 = polyp. of rectum or colon, 7 = pellagra, 8 = ulcer debilit., 9 = thrombosis, 10 = low blood-albumen and edema, 11 = nephritis, 12 = watch-glass-nails, 13 = ileocecal intussusception, 14 = symptoms from the liver, 15 = enlargement of the spleen, 16 = skin eruptions, 17 = cancer of colon.

**Follow up condition:**

A = free from symptoms since at least 2 years.

B = with symptoms during the last 2 years but not invalidated by follow up exam. (See text.)

C = actively ill, invalidated.

D = Died.

**Degree of severity:**

I = Slight (generally not invalidated).

II = Medium severity (Invalidated some part of observation period).

III = Serious (invalidated generally at least 1 year of observation period).

Table 1 (cont.)

No.	Med. hist. record no.	Sex	Age at onset of disease	Rectoscopy	X-ray exam.	Haemoglobin % min. value	S.r. cum hair max. value
1	Sam. 174/39	♂	5	II	III	46	40
2	KLB 493/29	♂	2	II	II	42	33
3	Sam. 512/44	♂	7	—	—	35	38
4	Norrt. 514/26	♂	11½	I	—	50	33
5	KLB 607/44	♂	7	III	II-III	69	55
6	KLB 1056/39	♀	14½	III	I	65	31
7	KS 55/40	♀	12	III	II	40	10
8	A.S. 397/40	♂	2½	—	I	90	27
9	KLB 759/34	♀	7	III	IV	40	23
10	KLB 176/36	♂	6	—	—	73	39
11	Sachs 499/44	♀	5½	III	—	57	31
12	KLB 175/43	♀	11	III	II	57	45
13	KLB 321/38	♀	4	I	I	42	83
14	Norrt. 652/44	♀	5	—	III	50	62
15	A.S. 22/29	♀	5	?	III	65	10
16	KLB 826/37	♂	6	I	IV	38	23 (80)
17	Norrt. 1484/44	♂	2½	III	III	60	46
18	KLB 180/19	♂	4	III	I	24	9
19	KLB 441/45	♀	2	III	III	68	50
20	Norrt. 473/37	♀	4	III	III	88	24
21	KLB 706/40	♂	5	—	III	60	55
22	KLB 190/44	♀	10½	II	III	77	95
23	Lund 579/32	♂	1½	—	I	30	52
24	KLB 142/42	♂	2	II	—	76	22
25	Sam. 775/43	♂	1	III	III	56	54
26	Gbg 1582/41	♂	9	I	II-III	75	17
27	Lund 707/45	♂	2	III	I	100	20
28	Norrt. 1027/45	♂	5	II	III	76	30
29	A.S. 887/38	♂	1	II	III	45	65
30	KLB 157/44	♂	1½	III	II-III	68	50
31	KLB 705/46	♂	3½	—	II-III	54	37
32	Norrt. 1315/42	♂	6½	I	—	87	0
33	KLB 585/35	♀	3½	III	IV	73	35
34	KLB 1052/39	♀	7	—	IV	69	29
35	KLB 442/41	♂	1½	—	II	88	12
36	Sam. 7/45	♂	6½	—	—	74	60
37	KLB 972/37	♂	8	II	II-III	85	14
38	Sam. 450/40	♀	10½	—	—	84	21

Table 1 (cont.)

Complications	Chemo-therapy	Immed. result	Period of obs. yrs	Time since last relapse yrs	Follow up condition	Degree of severity
0	1, 5, 13	—	8	now	C	III
2, 14	0		20	12	A	II
0	1	+	2½	1½	B	II
1	1	+	20½	1	B	III
0	1, 8, 14, 15	+?	4	now	B	II
0	5	+	7½	6	A	II
1, 11	1, 3, 11	+	7½	½	B	III
0	0		8	4	A	I
6	1, 5	—	12	1	B	III
16	0		11½	½	B	II
0	1, 3	—	4	2	A	II
0	1, 7, 12	+	4½	½	B	II
1, 5	1, 13	—	9	3½	A	II
8	3, 4, 6, 7, 8	+	3	now	D	III
0	0		½	now	D	III
(80)	7	+	10	now	C	III
0	1, 3, 8	+?	2½	½	B	I
9	0		6½	now	D	III
0	4, 8, 12, 15	+	2½	1½	B	II
0	0		10½	8	A	I
0	1, 5	+	7½	2	A	II
1, 12	1, 4, 14	+	4½	½	B	II
1	0		15½	3½	A	II
0	0		5	3	A	I
0	1, 5, 8, 13, 14	—	4½	now	D	III
0	1	+	6	1	B	II
0	0		8	1½	B	II
14	1, 3, 7, 8	—	6	½	B	II
1	1, 5	+	11	½	B	II
0	0		2½	1½	B	I
0	14	+	3	½	B	II
0	3	+	4½	3½	A	I
1	1, 3, 5	—	12½	1	C	III
0	0		11	6½	B	III
0	0		7½	1	B	II
1, 14	1	+	2½	now	B	II
1	1	+	7	now	B	II
0	0		6½	5½	A	I

Table I (cont.)

No.	Med. hist. record no.	Sex	Age at onset of disease	Rectoscopy	X-ray exam.	Haemoglobin % min. value	S.r. mm/I hour max. value
39	KLB 871/46	♀	9	II	I	40	93
40	KLB 422/35	♀	1-2	III	III	38	—
41	KS 969/40	♀	5	II	III	55	60
42	KLB 52/44	♂	3	I	I	68	77
43	KLB 544/35	♀	2	I	III	30	34
44	Sam. 385/41	♂	4	I	I	45	55
45	KLB 870/35	♀	3½	III	II	78	14
46	KLB 354/25	♀	3½	I	—	60	—
47	Norrt. 802/38	♂	3	—	—	33	41
48	KLB 257/45	♂	12½	I	II	40	48
49	KLB 831/41	♂	8½	II	II	79	10
50	KLB 1238/44	♂	6½	I	II	80	9
51	Sam. 829/43	♀	12½	II	III	72	80
52	KLB 859/36	♂	4	I	III	43	40
53	Sam. 814/34	♂	8	I	—	—	38
54	KLB 938/40	♂	4	—	—	82	24
55	Gbg 1425/39	♂	1	—	II-III	79	22
56	KLB 403/46	♀	8½	II	III	67	22
57	Norrt. 46/47	♂	2½	—	—	70	—
58	KLB 243/43	♀	4	III	—	70	45
59	KLB 36/39	♀	8	?	II	87	12
60	Sam. 598/43	♀	2½	—	—	65	40
61	KLB 537/44	♀	2½	?	II	83	35
62	Sam. 609/40	♀	6½	III	II-III	93	42
63	KLB 319/34	♂	1	II	II-III	65	40
64	Gbg 1164/40	♀	1	—	I	32	34
65	Gbg 1167/45	♀	1	II	II-III	93	10
66	KLB 149/46	♂	3	III	II	38	67
67	KLB 945/38	♂	6	III	III	50	43
68	KLB 542/42	♀	3	III	—	81	20
69	Norrt. 1087/43	♀	4	III	III	40	49
70	KLB 1203/41	♂	1	II	II	64	22
71	KLB 383/28	♀	2	—	—	40	—
72	Sam. 28/38	♀	8	I	III	43	80
73	Norrt. 409/28	♂	7	—	—	50	—
74	KLB 1045/38	♂	7	—	—	23	68
75	KLB 556/32	♂	5	III	III	81	41

Table 1 (cont.)

Complications	Chemo-therapy	Immed. result	Period of obs. yrs	Time since last relapse yrs	Follow up condition	Degree of severity
3	0	1, 14	+	1 $\frac{1}{2}$	B	II
2	12	1	+	20	now	B
30	3	1, 5	+	10	A	II
17	0	4, 12	+	3 $\frac{1}{2}$	now	B
3	2	1	-	16 $\frac{1}{2}$	now	C
55	1	1	+	6 $\frac{1}{2}$	B	II
24	0	0	-	12	A	I
-	16	0	-	21	A	I
41	14	1	-	9	3 $\frac{1}{2}$	A
18	2	1, 4, 6, 8, 12, 14, 15	+	2	now	C
10	0	0	-	6	A	II
9	0	1	+	3 $\frac{1}{2}$	now	B
80	2	1	+	3 $\frac{1}{2}$	now	D
40	16	0	-	10 $\frac{1}{2}$	B	II
38	0	0	-	12 $\frac{1}{2}$	11 $\frac{1}{2}$	A
24	0	0	-	6 $\frac{1}{2}$	B	I
22	5	0	-	12	5	A
22	0	1, 14	+	11 $\frac{1}{2}$	now	B
-	0	0	-	20 $\frac{1}{2}$	18	A
45	0	1	+	7 $\frac{1}{2}$	1 $\frac{1}{2}$	B
12	1	0	-	8	5 $\frac{1}{2}$	A
40	0	1	+	4	1 $\frac{1}{2}$	B
35	0	1	+	2 $\frac{1}{2}$	2	A
42	14	0	-	6	5	A
40	0	1	+	12 $\frac{1}{2}$	3 $\frac{1}{2}$	A
34	14	5	+	6	now	D
10	0	12	+	16	now	C
67	1	14	-	11 $\frac{1}{2}$	B	II
43	0	1, 3	-	8	1	B
20	0	0	-	5	4	A
49	0	1, 3, 4, 6, 11	-	4 $\frac{1}{2}$	B	II
22	1, 9	0	-	13	B	II
-	1, 5	0	-	1	now	D
80	18	0	-	9	B	II
-	1, 14	0	-	18 $\frac{1}{2}$	9	A
68	9, 14	1	+	8	4	B
41	0	1	+	14 $\frac{1}{2}$	B	II

Table 1 (cont.)

No.	Med. hist. record no.	Sex	Age at onset of disease	Recto-scopy	X-ray exam.	Haemoglobin % min. value	S.r. mm/l hour max. value
76	L 296/34	♀	2	—	II?	40	—
77	Ö 586/44	♀	2½	II	III	80	18
78	KLB 629/47	♂	3	I	II	80	2
79	Gbg 1302/43	♀	2	II	III	45	22
80	Lin. 27/35	♂	10½	I	III	35	45
81	Gbg 1151/45	♂	8	III	III	71	44
82	J 433/46	♂	7½	III?	I	91	31
83	Gävle 229/46	♂	1½	I	—	47	—
84	Gävle 8/47	♀	13	II	II	69	26
85	Gävle 29/45	♂	10	III	II-III	55	40
86	Gävle 7/42	♂	10	I	IV	51	35
87	Boden 158/43	♂	2	I	III	93	39
88	Boden 138/43	♂	1½	—	III	—	—
89	Krist. 342/44	♀	?	II	III	45	18
90	Krist. 614/44	♀	2	I	I	54	52
91	Krist. 40/41	♂	1½	I	II	77	15
92	Norrt. 407/46	♂	12	—	II	50	23
93	Norrt. 856/46	♂	7	III	II	66	50
94	Norrk. ?/45	♂	4½	—	II	67	26
95	Karls. 299/46	♂	7	I	I	62	20
96	Karls. 164/47	♂	10	I	II	70	—
97	Karls. 218/46	♀	1½	I	III	66	—
98	KS 1741/42	♀	11	II	IV	56	64
99	KS 984/46	♂	10	I	—	85	47
100	KS 1619/45	♀	10	II	IV	60	40
101	KS 1472/46	♂	10	III	I	55	45
102	KS 2198/44	♀	14	III	IV	40	77
103	KS 2109/44	♂	14	II	III	88	7
104	KS 1332/44	♀	11	II	—	68	54
105	KS 263/44	♀	9	III	III	65	47
106	KS 1962/43	♂	8	II	III	70	24
107	KS 779/44	♂	14	I	II-III	80	12
108	Lund 132/31	♂	5	III	IV	74	45
109	KS 2097/45	♀	9	II	III	75	20
110	KS 1432/45	♀	14	II	III	80	15
111	KS 2438/44	♂	13	II	—	60	25
112	KS 435/33	♂	7	I	IV	68	14
113	KS 227/30	♀	10	III	III?	70	6

Table 1 (cont.)

Complications	Chemo-therapy	Immed. result	Period of obs. yrs	Time since last relapse yrs	Follow up condition	Degree of severity	
5	0		3	now	?	II	
18	8	+	2½	1	B	II	
2	0		½	now	B	I	
22	0, 1, 3	+	6	3½	A	II	
45	0		12	11	A	II	
44	5, 12	+	5½	1	B	II	
71	1, 6, 10, 12	+	1	½	B	I	
—	1	+	1	now	B	I	
26	0, 1, 7	+	1	now	B	I	
40	14, 1, 12	+	2½	½	B	II	
35	0, 1, 8	+	5½	1	B	II	
39	0, 1	—	8½	2½	A	I	
—	1	—	4	2	A	I	
18	0, 1, 8	+	>2½	½	B	II	
52	2, 1, 3, 12, 13	—	2½	now	C	III	
15	7, 14, 1, 3	—	10½	1	B	II	
23	15	0	3	¾	B	II	
50	0, 1, 6, 7	+	¾	¾	B	II	
26	11, 16, 7	+	½	½	B	I	
20	0, 1	+	1½	½	B	I	
—	0, 1	+	¾		B	I	
—	14	1	+	1½	½	II	
64	2, 3, 6, 9, 1, 4	+	9	now	D	III	
47	0, 1	+	1½	¾	B	I	
40	0, 1	+	11½	2	A	II	
45	13	1	4½	¾	B	II	
77	14, 1, 14	+	13½	1½	B	III	
7	0, 1	+	9	now	B	II	
54	0, 1, 5	+	3	2	A	I	
47	0, 1	—	7½	2	B	III	
24	9	1	4	now	B	II	
12	0, 1	+	½	now	B	I	
45	3, 1, 8, 13	+	18½	now	C	III	
20	0, 1, 2	+	3	1	B	I	
15	0, 13	+?	4	½	B	II	
25	0, 1, 8	+	4	½	B	II	
14	1, 6, 14	1, 4, 5, 6, 7, 14	—	14½	½	B	III
6	0, 5, 13	+	15	½	B	III	

Table 1 (cont.)

No.	Med. hist. record no.	Sex	Age at onset of disease	Rectoscopy	X-ray exam.	Haemoglobin % min. value	S.r. (min. hour index) value
114	KS 99/40	♀	13	III	III	50	6
115	KS 579/44	♂	7	II	III	54	1
116	KS 2148/45	♀	11	III	III	48	8
117	KS 1293/40	♂	10	III	—	50	5
118	KS 1413/40	♀	7	II	III	70	9
119	KS 1146/41	♂	2½	III	IV	57	7
120	KS 1723/41	♂	12	II	II-III	85	4
121	KS 438/42	♀	10	III	III	95	3
122	KS 1832/43	♂	7	II	III	83	7
123	KS 18/40	♂	11	III	III	22	2
124	Ep. /47	♀	6	I	I	70	0
125	Falun 50/46	♂	11	II	III	58	0
126	Ep. 4393/47	♂	12	II-III	—	85	18
127	KLB 617/46	♀	7	III	III	68	37
128	KLB 769/47	♀	6	II	II	70	38
129	KLB 417/48	♂	1½	II	I	75	26
130	KLB 378/48	♂	4	III	I	75	46
131	Ersta 1359/46	♂	7	III	II?	71	30
132	Ep. /48	♂	8½	II	I?	80	15
133	Norrt. 85/48	♀	10	I	III	72	40
134	Sachs 830/47	♂	8	?	III	79	—

cases have been discussed previously in papers by Professor SVARTZ and will continue to be followed up by her. They have been included here in order to make the picture of u. c. in children as complete as possible. The other 31 cases have been treated most of them during the last 5 years in children's wards in the province. The author wishes to express his gratitude for provision of materials to Professors Gyllenswärd, Malmberg, Siwe and Wallgren and Drs Brandberg, Hamne, Herlitz, Hermansson, Jelke, Karlström, Kostman, Lindberg, Magnusson, Selander, Ström and Åkerrén.

The following criteria have generally been required for the diagnosis: long period of illness (at least half a year and as a rule longer; 1 case (No. 107) was followed only 3 months but showed

Table I (cont.)

Complications	Chemotherapy	Immed. result	Period of obs. yrs	Time since last relapse yrs	Follow up condition	Degree of severity	
6, 11	1, 5, 8	—	5	now	C	III	
1, 10	1	+	8½	now	C	III	
8, 14	1, 5, 6	+	5½	now	D	III	
5	14, 17	1, 5	+	11	now	D	III
9	1, 3, 10	1, 3, 5	+	5½	½	B	II
7	0	1, 5	—	7½	now	C	II
4	2, 14	1	+	10	½	B	II
3	0	1	—	10	2	A	II
7	0	1	+	4½	1	B	II
2	9	1, 2, 5	+	11½	2	A	III
14	7	—	½	now	B	I	
0	—	1, 3, 5	+	2½	now	B	II
18	2, 10	1, 6	+	½	now	B	III
17	0	1, 14	+	2½	1½	B	II
38	14	1, 12	—	2½	½	B	II
26	0	8	+	8½	½	B	I
16	0	8	+	½	now	B	I
30	0	3	—	1	½	B	I
15	0	1	+	½	½	B	I
30	0	7, 8, 9	+	½	now	B	I
—	0	1, 4, 11	+	1	½	B	I

a typical picture of the disease, including rectoscopy), accompanied by purulent bloody evacuations (generally diarrhea), typical rectoscopy and/or X-ray picture, and a bacteriological feces culture which has excluded the possibility of salmonella and dysenteric infection. 25 of my cases do not fully meet these requirements. In 10 cases rectoscopy and X-ray examination were either not carried out or at the time of examination showed normal conditions. In these, however, the clinical course of the disease was so typical that it was nevertheless possible to diagnose u. c. In 15 cases dating from earlier years there are no data on bacteriological feces culture in the *acute* stage. Since these cases were all of long duration and in other respects quite typical, and as similar conditions induced by salmonella or

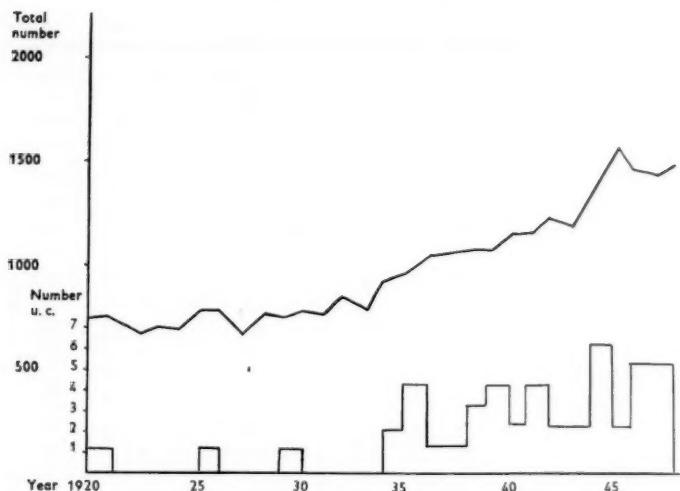


Figure 1. New cases of u.c. at Kronprinsessan Lovisas Barnsjukhus, Stockholm (columns) in relation to all cases treated at the medical department (line).

dysenteric bacteria have not hitherto been described from Scandinavia, they have also been included in this survey. Milder forms of colitis, tuberculosis of colon, primary polyposis and cancer have been excluded by differential diagnosis based on clinical observation of the course of the disease.

131 cases have been followed up. Of the 3 that were not given later examinations 1 case was followed for 5 years after first appearance of the disease, and the 2 others for shorter periods.

Fig. 1 shows the occurrence of fresh cases of u.c. in proportion to the total number of patients treated since 1920 at Kronprin-

#### *Diagram I.*

Course of disease in all cases observed at least  $2\frac{1}{2}$  years (all fatal cases).

Whole column = age in years by follow up.

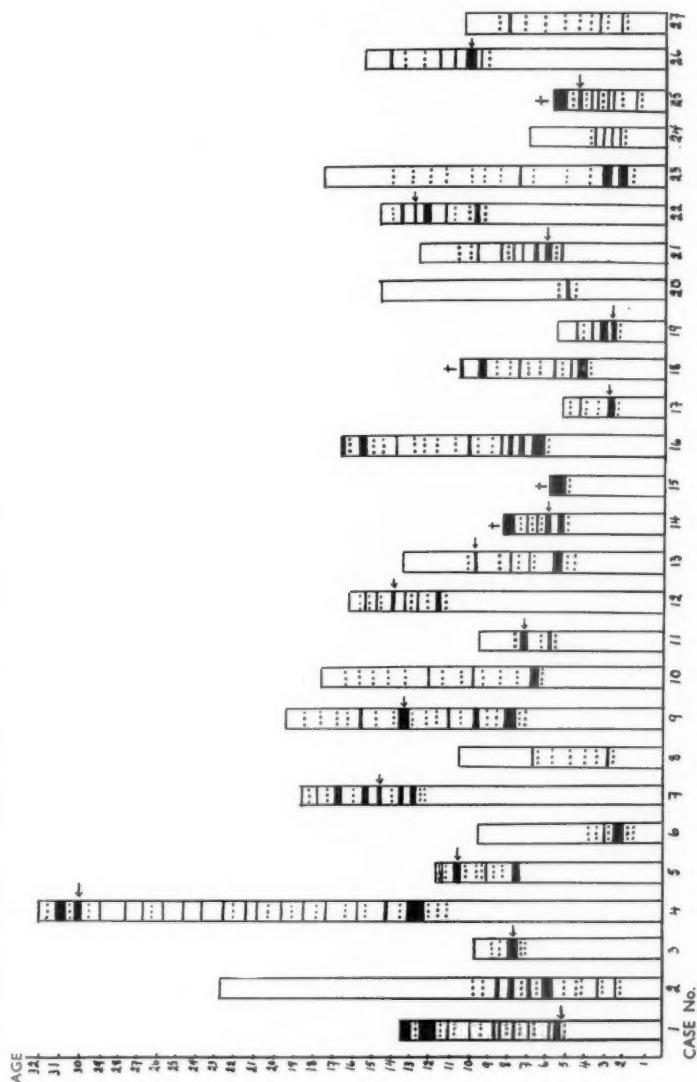
Black parts = periods of invalidating symptoms.

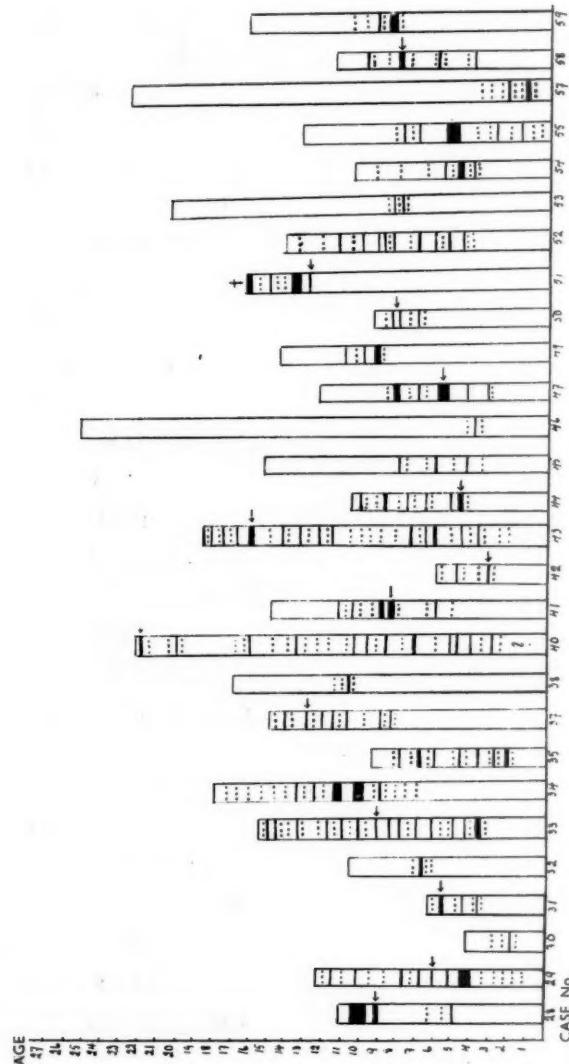
Pointed parts = periods of symptoms not invalidating.

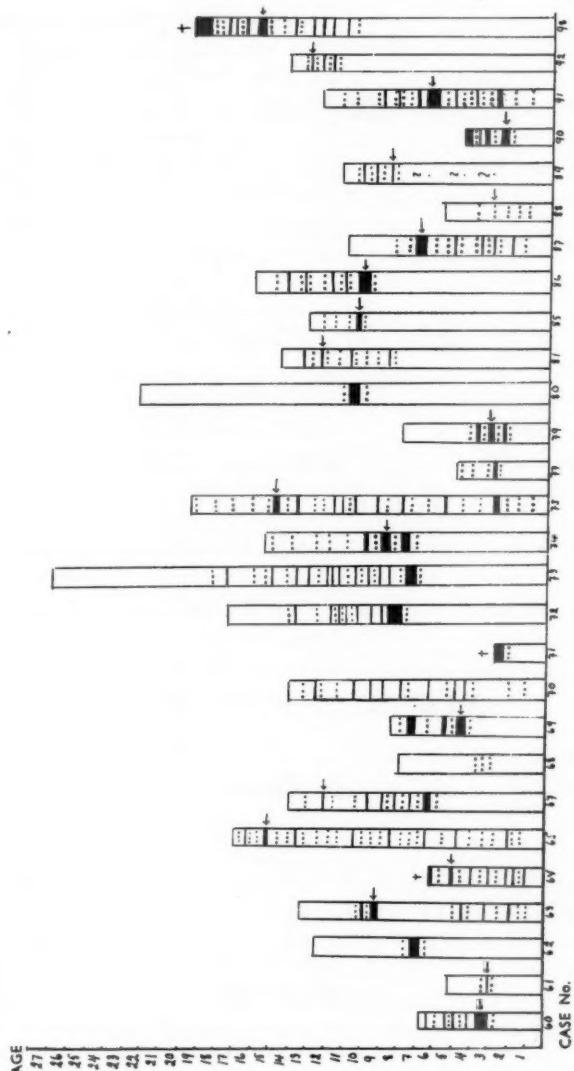
Unfilled parts = symptomfree periods.

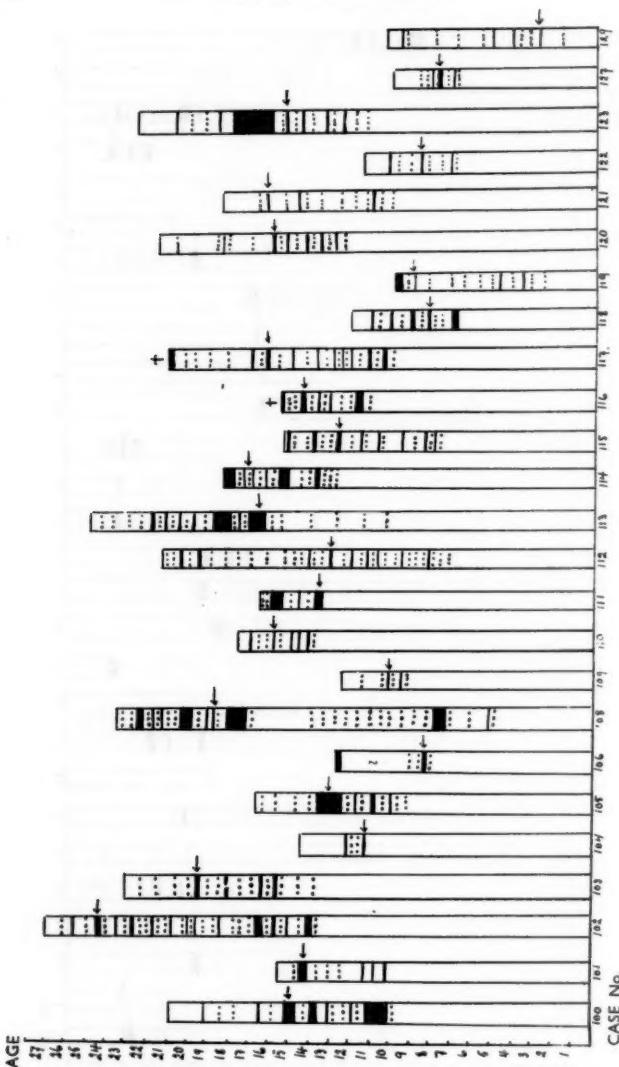
Arrow = time for first treatment with sulfanilamides compounds.

† = died.









sessan Lovisa's Childrens Hospital. We find a clear increase both absolute and relative in the number of cases of u. c. in recent years. To prevent cases dating from earlier years from being captioned as chronic colitis or spastic colitis, the medical history records of these cases have also been checked, but not a single fresh case of u. c. was found. Nor is there any reason to attribute the increase in the number of cases to the fact that they have been concentrated in our hospital in recent years; the disease has also become more common in other children's hospitals in Stockholm.

The material comprises 78 boys and 56 girls.

It has been possible to obtain a more or less definite idea of the social classes from which the patients came in most cases. Only 4 came from manifestly poor homes.

The psychical environment is more difficult to judge on the basis of the material available. In earlier years there was not sufficient interest in that aspect of the cases. Nevertheless, we find that 25 cases lived in a decidedly poor psychological environment. In this category are included children of divorced parents, children of very unhappy marriages, refugee children, children born out of wedlock and children who ceased to be the «idols» of their parents after the birth of another child. In view of FAXÉN's investigations into the manner in which children who have long been alone and subsequent brothers or sisters react to infectious diseases, it may be observed that 54 cases were only children or first-born, while 45 were intermediate children or the youngest in their families. With regard to the rest this circumstance was not known.

In 114 cases there are data on the *hereditary conditions*, though the particulars are often incomplete. In 77 cases it is stated that the heredity was of no interest. In 12 cases (9 %) there had been more or less serious intestinal affections among the nearest relatives. 2 brothers suffering from u. c. are included in the material. In 15 cases very close relatives had suffered from allergic diseases, in 11 cases from nervous or mental diseases, and in 4 cases from disturbances in the internal secretions.

In 108 cases there was information concerning the delivery.

It was normal in 103 cases, while 5 were delivered with forceps. — In 97 cases the birth weight was known, being over 2 500 gr in 94. The *method of feeding* was known in 98 cases; in 68 the child was breast-fed for more than 6 months, in 17 for from 2 to 6 months, and 5 had mixed feeding from birth. Only 8 cases had never had mother's milk. Prior to falling ill 113 cases had developed normally both physically and mentally. 16 had been physically delicate prior to the onset of the disease, but only 5 had been backward mentally (2 of these were also physically delicate). At least 6 (see below) had previously shown symptoms of neuropathy and 5 had had nocturnal enuresis. 2 had had pseudoeroup and 1 acetone vomiting. In 94 cases an inquiry was made into allergic symptoms prior to the onset of the disease: of these 68 had not shown any such symptoms, while 25 cases (26.6 %) were stated to have had them (asthma 4 cases, eczema 7 cases, asthma and eczema 1 case; hay fever, urticaria, strophulus 10 cases, other supersensitivity 4 cases).

Most cases had normal evacuation prior to falling ill. 15 had had a tendency to loose movements and 8 had frequently had constipation.

With regard to diseases suffered prior to the onset of u. e., the material shows no abnormal frequency or type distribution except for infections of the upper respiratory tract, which occurred with striking frequency — in 52 cases. In many cases, however, definite data were not obtained as to whether these occurred prior to the onset of u. e.

*Distribution by age* among fresh cases of the disease is shown in Fig. 2. In rural districts a number of older children were probably treated in wards for adults, whereas in Stockholm practically all of the children were treated at least part of the time in children's hospitals. As the Figure shows, even among cases that fell ill in Stockholm, the majority became ill between the ages of 2 and 6. — The *time of year* in which the cases became ill was known in 105 cases; and shows even distribution.

In 132 cases it was possible to determine whether or not the children fell ill in conjunction with some other disease. 110 cases contracted u. e. without any connection with any other

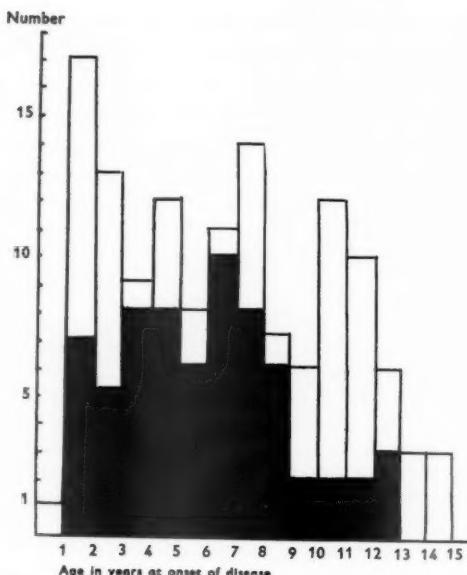


Figure 2. All cases grouped according to age at onset. Cases from Stockholm in black.

disease. In the following cases it was indicated that they had fallen ill in conjunction with the diseases mentioned:

parotitis .....	1
scarlatina.....	1
scarlatina with jaundice.....	1
measles.....	1
measles with jaundice.....	1
jaundice (hepatitis).....	1
severe infection of the upper respiratory tract.....	8
dysentery.....	1
simultaneous case of diarrhea in the vicinity.....	5
smallpox vaccination.....	1
infected skinwound.....	1
<hr/>	
	Total 22 cases

In 127 cases the manner in which the patient fell ill was known. Of these, 104 (81.9 %) had shown more or less insidious symptoms

starting with frequent loose evacuations. These cases were at the outset afebrile or subfebrile and not invalidated at all or only gradually. This group includes 14 cases (11 %) in which the initial symptom was only bleeding on or after normal evacuation. 10 of these subsequently had diarrhea, while 4 others had the disease only slightly with a good prognosis. Only 11 cases (8.7 %) contracted the disease acutely with a temperature of over 100° F. and severe diarrhea with blood and mucus. 12 cases (9.4 %) contracted the disease subacutely in conjunction with some other disease.

3 typical cases are described below, including an instance of an acute onset, one of an insidious attack, and one of a mono-symptomatic attack.

*Case no. 21.* Kronprinsessan Lovisa's Children's Hospital no. 706/40. Boy. Weight at birth 3.6 kg. Mixed feeding for 9 months. Normal development. Frequent infections of upper respiratory tract. At age of 5 became acutely ill with fever, frequent loose evacuations mixed with blood, and stomach ache. Temporary improvement as result of diet. Remittent course. Not treated in hospital until 6 months after contracting disease. Upon admission to hospital general condition fair, thin, slight anemia, increase in sedimentation rate, loose bloody bowel movements. Colon X-ray showed sparse, largely suspended hastration in sigmoid flexure, descending and transverse colon. Treatment confinement to bed, diet, extra vitamins, blood transfusion iron and salazopyrine, without striking effect. Gradually the patient improved, but had several relapses, particularly in connection with infections of upper respiratory tract. Several periods in hospital. After several years usually not invalidated. Subsequent examination 7 1/4 years after onset of disease showed no serious relapse in preceding 2 years, though occasionally pale blood on feces; on follow up, incl. rectoscopy, found to be free of symptoms.

*Case 17.* Norrtull Hospital No. 1484/44. Boy. Heredity normal. Normal delivery weight at birth 3 750 gr. Breast fed for 5 months. Normal development. Frequent infections in upper respiratory tract. Constipation at age of 2 1/2, then gradually loose and increasingly frequent evacuations, after a time bloody. By degrees effect became general — pale, irritable, tired, abdominal pains. Upon admission to hospital after month's illness somewhat thin, no pathological symptoms from internal organs, no anemia, moderate increase in sedimentation rate. Bloody feces with abundance of iodophile substance. Rectoscopy showed swollen, edematous mucous membrane. Colon X-ray showed sparse, irregular hastration. Treatment (confinement to bed, diet, blood

(transfusion, sulfathiazole) resulted in improvement. Subsequently several relapses, especially in connection with upper respiratory tract infections, moderate anemia. Several periods in hospital; patient also treated with salazopyrine and improved, but had relapses later. Upon follow-up examination  $2\frac{1}{2}$  years after onset of disease, general health good, 2 semi-solid, at times bloody, evacuations per diem, moderate anemia.

*Case 68.* Kronprinsessan Lovisa's Children's Hospital No. 542/42. Girl. Heredity and delivery normal. Weight at birth 3 600 g. Breast fed for 3 months, after which mixed feeding for 3-4 months. Normal development. Previously quite healthy with normal evacuation. At age of 3 red blood on feces, which were otherwise normal in colour and consistency. Later sometimes evacuation 3-4 times daily. Otherwise no trouble; appetite and weight normal. Intermittent course, hospital treatment after 6 months' illness. On admission unaffected, well nourished, no pathologic symptoms shown by internal organs (excl. rectum), no anemia, moderate leucocytosis and increase in sedimentation rate. Rectoscopy showed mucus-covered sores and abundant bleeding in mucous membrane.

Treatment: confinement to bed, mixed diet, extra vitamins. Discharged from hospital after 10 days. After discharge rapid improvement. Blood in feces not subsequently observed. At times 3 evacuations per day, semi-solid or solid. When re-examined including rectoscopy 5 years after onset of disease patient was free of symptoms.

According to the anamnesis the most important and commonest symptom was frequent and/or loose evacuations (only 4 cases were without this symptom — see above). 23 cases had had loose evacuations alternating with constipation over a long period. At least 20 cases had at some time or other had blood or mucus on otherwise normal feces. In 17 cases the feces had passed involuntarily. Even considering the fact that children cannot indicate pains with any exactness, there does not appear to have been conspicuous pain in the majority of cases. In 34 mention is made in the medical history records of abdominal pains but no details are given, while in 19 abdominal pains round the umbilicus without any connection with meals are mentioned. In 10 cases it was indicated that the patient complained of trouble with flatulence, and in 17 cases with tenesmus. As a rule the pains occurred in acute attacks of u.c. Vomiting occurred

frequently in only 28 cases in this material. In most cases the appetite was good at the beginning of the illness, nor did it subsequently deteriorate in the slight and moderately severe cases. In 14 relatively severe cases of long duration the appetite is indicated as being strikingly good. In spite of good appetite, however, most of the patients became extremely thin. The loss of weight was greatest in the group in which the entire colon and the distal part of the ileum were attacked and least in the group in which only the rectum was attacked. In many cases the patient maintained or increased his weight while in a sub-chronic stage.

The *growth* in height was normal in 112 out of the 120 cases in which it could be judged, while in 8 cases it was delayed. These cases were seriously ill, the prognosis being relatively unfavourable (see below). Each one of the 5 who underwent X-ray examination had changes in the entire colon (including rectum), and one case also had changes in the terminal iliac loop.

Owing to incomplete medical history records, the temperature could not be determined in 9 cases. Among the other 125 there were 90 cases that were as a rule sub-febrile, 22 as a rule afebrile and 13 who occasionally had a high temperature. A number of cases with ulcerative proctitis and changes in the entire colon were also afebrile. The cases which occasionally had a high temperature suffered as a rule, though not always, from more serious disease with a poorer prognosis (see below) than the cases which were generally afebrile.

In regard to *psychological symptoms*, it is an open question whether these should be regarded as part of the primary pathological picture or numbered among the complications. The earlier records have practically no notes on psychological symptoms. In 20 cases in all it is pointed out that the patient was easily irritated, depressed, »peevish» or »nervous».

111 patients were at one time or other examined *rectoscopically*. In 104 of these cases pathological changes were indicated, while in the other 7 the examination had either been made at an early stage of the disease or else had proved technically unsuccessful. The material is divided into 3 groups according to the degree of severity:

Group I: hyperemic, swollen, easily bleeding mucous membrane = 33 cases;

Group II: hyperemic, «woolly» mucous membrane, often coated with pus, mucus or fibrin = 32 cases;

Group III: cases which, besides the above-mentioned changes, showed ulcerous mucous membrane (some of these also had scars from old ulcers) = 39 cases.

In 109 cases the *colon* had been *X-rayed* (contrast enema). A section of the intestine was considered to be attacked if the passage of the contrast enema was abnormally rapid and haustration was irregular or suspended and/or the mucous membrane was atrophic or ulcerous. In 73 cases (66 %) the entire colon, or large parts thereof, was described as «lead pipe», frequently with small notches in the contour of the mucous membrane. Following the X-ray examination the material was divided into 4 groups according to the spread of the disease:

(One must remember, however, that many cases were not followed regularly with X-ray.)

Group I: only the rectum attacked (normal colon X-ray) = 12 cases;

Group II: rectum and colon up to and including the descending colon attacked = 21 cases;

Group III: rectum and the entire colon attacked = 64 cases;

Group IV: rectum, colon and terminal ileac loop attacked (the same changes in the terminal ileac loop as in the colon: rigid, possibly notched contour, constricted lumen and mucous membrane irregular in relief) = 9 cases.

In 3 cases the result of the X-ray examination was uncertain.

In 4 cases X-ray examination indicated changes but rectoscopy showed normal conditions. In these rectoscopy was undertaken once only at the onset of the disease. Otherwise the cases do not differ from the others, so that one would not venture here to assume segmental u. c. (BARGEN). Table 2 gives a summary of the spread of the disease in relation to its severity and prognosis (see also below).

In all cases except 2 hemoglobin and red blood corpuscles were examined. In most cases the blood values were followed

Table 2.

X-ray examination in relation to prognosis and degree of severity and the prognosis and degree of severity for cases with liver-symtoms. Only cases observed at least  $2\frac{1}{2}$  years.

X-ray exam.	Num-ber	Follow up condition				Degree of severity		
		A Free from symptoms at least 2 yrs %	B Unwell but not invalid %	C Inva- lided %	D Died %	I Slight %	II Medium severity %	III Se- rious %
Rectum.....	5	, 80	20	0	0	40	60	0
Rectum and lower part of colon .....	11	45.5	54.5	0	0	36.4	54.5	11
Rectum and entire colon .....	50	24	56	10	10	10	64	26
Rectum, colon and lower part of ileum	11	9.1	45.5	36.4	9.1	0	27.3	72.7
Cases with liver-sym-toms .....	20	20	50	10	20	5	60	35

by frequent examinations, so that the minimum value indicated in each case in Table 1 is probably reliable. In Table 3 the minimum hemoglobin value is put in relation to the degree of severity of the disease, its spread and the condition of the patient upon follow-up examination (see also below for discussion and conclusions).

As a rule the anemia was hypochromic but occasionally it was normochromic. In 123 cases there were particulars concerning the number of white blood corpuscles and generally of the differential count as well. 95 of these had, occasionally at least, leucocytosis ( $\geq 9\,000/\text{mm}^3$ ) and/or shifting to the left. In 26 cases the white blood picture was normal on the only occasion or the few occasions on which it was examined. Eosinophilia of  $\geq 7\%$  was observed in 17 cases, in 6 of which there was a record of hereditary and/or anamnestic allergy.

In 126 cases at least 1 value is given for the sedimentation

rate. In the majority of cases this has been followed constantly. In Table 1 the maximum value of sedimentation rate is given. A table drawn up on the same lines as Table 3 shows that the sedimentation rate has a more indefinite relationship than the hemoglobin value to the degree of severity of the disease, its spread, and the prognosis.

*Eucald's test breakfast* was given in 52 cases. In 39 the result was normal, while in 13 hypochylia was observed. In 2 cases it gave normal values at the onset of the disease, but subsequently indicated hypochylia. A histamine test was tried in 2 of the hypochylie cases; the result was normal.

The *feces* were examined repeatedly in all cases. The anamnestic data discussed above were verified. Cases suffering only from proctitis had red blood smeared on the outside of the feces. If the colon was also attacked, the blood was red or dark and was mixed with feces, mucus and pus. In 2 cases there was abundant bleeding from the rectum; one of the patients died and the other recovered. There are no reports that in cases in which the ileum was also attacked the stools were particularly large. Microscopic examination of the feces was carried out in 91 cases. The most common change observed was an increase in the iodophile substance (iodophile bacteria, chlostridia and substance); this was indicated in 56, while in the other 35 the stools were normal in this respect. Signs of poor digestion (sharp-edged muscular remains etc.) were not observed in a single case.

*Bacteriological feces cultures* to exclude the possibility of salmonella and dysenteric infection were carried out in 119 cases, in the great majority several times, but always with negative results. In 42 cases an estimate was made of the relative occurrence of colon bacteria or cocci in the feces flora. In 25 of these (60 %) a substantial increase in the number of cocci (generally enterococci) in relation to the colon bacteria was observed.

In 53 cases the author himself made feces cultures<sup>1</sup> by the usual method in order to exclude the possibility of salmonella

<sup>1</sup> The bacteriological work was performed during the author's period of service in the Bacteriological Central Laboratory of the Hospital Direktorate, Stockholm. Physician in Chief: Professor H. Davide.

Table 3.  
Hemoglobinminimumvalue in relation to prognosis, degree of

Hemoglobin-value %	Number	Follow up condition			
		A Free from symptoms at least 2 yrs %	B Unwell but not invalidated %	C Invalidated %	D Died %
< 50	26	26.9	46.2	11.5	15.4
50-70	42	23.8	54.7	9.6	11.5
> 70	33	42.4	51.5	6.1	0

and dysenteric bacteria (Kaufmann's enrichment broth was used). In addition samples were cultivated aerobically and anaerobically on ascitic agar-agar and on blood agar as well as in Pike's enrichment broth for hemolytic streptococci. The results in relation to the condition at the time of the examination will be found in Table 4.

Table 4.

The fecal flora in different groups according to clinical condition.

Faecal flora rel.	Healthy	Unwell not invalidated	Ill, invalidated
No or a few cocci .....	7	2	0
More than a few but not 50 % cocci..	11	9	3
More than 50 % cocci .....	4	6	10
No or a few haemolytic colon bac....	12	9	4
Haemolytic colon bac. dominating ...	5	7	7

Thus it was found that among those actively infected by the disease at the time of the examination, the cocci usually dominated over the colon bacteria, and hemolytic colon strains (the hemolysing capacity determined on horse's blood agar-agar) occurred more frequently than in healthy subjects (according

3.  
severity and X-ray. Only cases observed at least 2½ years.

Degree of severity			X-ray					
I Slight %	II Medium severity %	III Serious %	1 Rectum %	2 Rectum a part of colon %	2 Rectum colon	4 Rectum co- lon a part of ileum %	Unknown %	
0	53.9	46.1	11.5	7.7	46.2	11.5	23.1	
11.9	54.8	33.3	2.4	7.2	45.2	14.3	30.9	
36.3	57.6	6.1	6.1	21.2	51.5	3.0	18.2	

to SJÖSTEDT and others the hemolytic coli bacteria are more pathogenic than the anhemolytic). The cocci were of different types, the most common were anhemolytic Grampositive cocci which grew in a »diplo» state or in short chains. Since they grew in 6.5 % saline solution these should probably come under the heading of enterococci. Most of the few which were tested were resistant to sulfathiazole and penicillin. The second most common type of coccus was the  $\alpha$ -streptococcus, which has not been exactly defined.

#### *Course and Complications*

In all the cases the course was more or less remittent or intermittent. In the diagram appended to Table 1 the course in each individual case is illustrated. The majority show gradual deterioration in the beginning, then occasional signs of improvement (right up to apparent health) interrupted by relapses. Severe exacerbations and deaths (see below) occurred at various times during the course of the disease. Not until a patient had been free of symptoms for 2 years was it unlikely that he would have a relapse (see below). The most common cause of relapse was indicated in 89 cases to be infection of the upper respiratory tract. At least 52 cases had such infections with striking frequency, in many cases even prior to the onset of the disease. Of 71 patients 25 had undergone abrasio and/or tonsillectomy.

Even long after the patients were symptom free they sometimes had frequent loose evacuations if they suffered from nasal catarrh or the like. In 21 cases faulty diet was indicated as a cause of deterioration in health; in 5 of these there was reason to suspect allergy to certain kinds of food, while among the remainder the deterioration was apparently caused by indigestible food (chiefly coarse vegetables). In 16 cases psychical causes of deterioration were observed in spite of the fact that, as has been said, the medical history records are often deficient in this respect.

It is frequently difficult to determine which of all the symptoms that appear during the prolonged course of the disease may be regarded as complications.

The following symptoms, which must be regarded as directly connected with the basic disease have occurred:

Thrombosis .....	6 cases
Perforated Colon (ascertained on post mortem).....	3    "
Perirectal Abscess .....	3    "
Rectal Polypus .....	3    "
Anal Eczema.....	1 case
Cancer of the Colon with Metastasis.....	1    "
Polyposis of the Colon .....	1    "
Anal Fistula .....	1    "

*Thrombosis* was localized in the femoral vein and/or the pelvic veins. In 4 out of 6 cases it was combined with severe anemia. It was a late complication (only one case had thrombosis during the first year of the disease, the rest suffering from it from 3—12 years after its onset). Case no. 74 has been published previously by LICHTENSTEIN, but it is recorded here again as because it is particularly interesting not least from a therapeutical standpoint.

*Case 74.* Kronprinsessan Lovisa's Children's Hospital, No. 1045/38. Boy. From age of 1 suffered from severe u. c. (see Table I with diagram). After 5 years acute deterioration set in accompanied by fever, vomiting and stomachich pains. Readmitted to hospital. Much affected with enlarged spleen, increasing thrombosis of the deep veins in the left leg and later right calf as well and increasingly pronounced vein markings on the thorax. Hemoglobin 30 %. At first deterioration in general state of health; edema and ascites set in. On a vital indication, 25 mg heparin

was injected intravenously every four hour for 7 days. Immediate gradual improvement of general condition; vein markings, edema and enlargement of spleen gradually receded. Colitis also improved by degrees and after intramuscular blood injections and administration of iron patient was able to leave hospital after 6 months. 5 years later he was re-examined. On the whole he had been well, though he had had an occasional loose evacuation when suffering from infections in the upper respiratory tract; as a rule he was not invalidated. Examination showed him to be in sound state of health and fairly strong; height and weight normal; slight eczematous changes on the calves, no pathological symptoms in internal organs; no anemia; evacuation normal (rectoscopy refused).

(One other case of thrombos was given heparin with good result.)

The cases of *perirectal abscess* and *rectal polypus* were of medium severity and of relatively long duration. The cases of *anal eczema* suffered from severe u. c. and were much troubled by that symptom. The cases attacked respectively by *cancer of the colon* and *polypus of the colon* both died (see below).

Of the other symptoms derived from the intestine which may be suspected of being complications we note 5 cases of prolapse of the rectum (of which 4 were of medium severity and 1 proved fatal). This symptom, however, also occurs in children with a healthy intestine and need not be associated with u. c. In all cases it appeared within the first year of the disease and the rectum recovered its position spontaneously. Further may be noted 1 case of ileocecal intussusception which may possibly have had some connection with the basic disease.

The connection between symptoms outside the intestine and the basic disease is often debatable.

In 3 cases (a minimum, seeing that the majority were not examined for this symptom) there occurred *low serum albumen with edema*, apparently a direct consequence of the basic disease. — *Symptoms in the joints* have been described in the largest series as an ordinary complication associated with u. c. (see above). Frequently these articular symptoms have not been described in detail, however, and their connection with the basic disease has not always been clearly established. It is striking to note how infrequently articular symptoms have occurred in the Scan-

dinavian material (MOLTKE, SVARTZ). In my own cases, articular symptoms occurred in 16 cases, in 9 of which symptoms in the form of pains, swelling of the joints and fever were definitely reported. 2 of these showed a polyarthritis picture (possibly there were 2 diseases involved). 5 other cases also had symptoms in several joints (hip, knee, foot and finger joints). 2 more had symptoms in a hip joint. 7 complained of pains and stiffness in the joints without any demonstrable swelling. In 6 of these there were symptoms in several joints (usually knee and foot joints). Articular symptoms occurred as a rule in a later stage of the disease (in 10 cases 5 or more years after its onset). A number of cases had relapses of trouble in the joints, but the articular symptoms had very little bearing on the prognosis and did not give rise to any permanent injury.

In 21 cases there were *liver symptoms* as follows:

Hepatitis.....	8 cases
Enlargement of Liver (possibly accompanied by enlarged spleen).....	8 *
Cirrhosis .....	2 *
Cholecystitis.....	2 *
Fatty Liver (p. a. d.).....	1 case

The cases of hepatitis presented the usual picture of infectious hepatitis; in 4 of them, however, the enlargement of the liver and/or the spleen lasted for a period of varying length after the recession of the disease. 4 of the cases occurred within the first 6 months of illness. The others occurred from  $1 \frac{1}{2}$  to 9 years after the patients first fell ill. Enlargement of the liver was not pronounced, though probably pathological. In 3 cases enlargement of the liver occurred within the first 6 months of the disease; in the other cases, during the first or second year. Cirrhosis made its first appearance in both cases about 5 years after the patient fell ill, and it proved fatal. Fatty liver was diagnosed in one of the cases that died after 9 years of illness; see, also, below. One case probably had cholecystitis at the commencement of the disease, while in the other case it made its first appearance about 1 year after the disease had set in. The prognosis in cases showing hepatic symptoms was relatively bad (Table 2).

Hepatitis, cirrhosis and cholecystitis (and possibly enlargement of the liver) may be diseases without any association with the basic disease. With regard to the first-mentioned, the patients had been in the hospital a long time and may have acquired an inoculatory or an alimentary infection there. On the other hand there may be a connection between these diseases and u. c. As mentioned above, injuries to the liver in cases of u. c. have been described previously. TUMEN, MONAGHAN and JOBB have indicated the probability of hepatic cirrhosis's being a complication of u. c. (several of their patients with u. c. in conjunction with hepatic cirrhosis were remarkably young). In the author's cases evidence of a connection between u. c. and injuries to the liver is also provided by the relatively high frequency of these injuries and by some cases in which the hepatic cirrhosis dominated the pathological picture, though with intestinal symptoms à la u. c. This was the case in the 2 following cases (not comprised in the material).

Med. hist. record Gothenburg Children's Hospital, No. 443/1941. Boy. Heredity normal. Delivery and weight at birth normal. At the age of 5 «intestinal catarrh», diarrhea and vomiting; better after some time. At the age of  $10\frac{1}{2}$  measles, followed by gradually increasing diarrhea mixed with blood. After about 2 mos., admitted to hospital. On admission somewhat affected, thin, sub-icteric, other signs of hepatic cirrhosis, strong sec. anemia; rectoscopy and X-ray examination typical of u. c. Treatment: confinement to bed, light diet, iron, vitamins and salazopyrine. Discharged improved in health. After discharge, normal evacuation, but increasingly handicapping symptoms of hepatic cirrhosis. Died in hepatic coma at age of  $15\frac{1}{2}$  — about 5 years after first appearance of intestinal symptoms, which were not conspicuous during last 2 years. Autopsy showed hepatic cirrhosis; colon showed lymph-follicle swelling in otherwise normal macroscopical picture.

Med. hist. record, Sachs Children's Hospital, No. 712/44. Boy. Heredity normal. Delivery and birthweight normal. Development normal. Healthy up to 9 mos. of age, when jaundice set in, lasting 2 months. Thereafter healthy up to age of  $7\frac{1}{2}$ , when child fell ill with frequent bloody, mucous diarrhoea. Taken to hospital after 1 week; upon admission thin, enlargement of liver and spleen, slight icterus; rectoscopy showed ulcerous mucous membrane. Treatment: confinement to bed, vitamins, sulfathiazol, last named without effect. On discharge from hospital showed improvement, but afterwards periods of deterioration

accompanied by fever and frequent loose evacuations. Gradual invalidism, severe anemia (Hb 45 %). Upon follow-up-examination more than 2 years later patient's general condition was poor; he was up but did not attend school; pale, thin, liver and spleen greatly enlarged, slight icterus, Hb 45 %, frequent loose, bloody evacuations.

Among the other symptoms outside the intestine which may be suspected of being complications (and which have previously been described as such) may be mentioned *aphthous stomatitis* (7 cases), *nephritis* (2 cases), *pellagra* (1 case) and *skin eruptions* (4 cases), but the connection between these symptoms and the basic disease appears to be uncertain.

No psychical symptoms have been included among the possible complications mentioned above. Part of the material has not been investigated sufficiently closely to bring these symptoms to light but it is evident that they occur often (in the form of irritability, «nervousness», depression, difficulties in adjustment etc.).

According to the above analysis, the number of cases with definite evidence of complications (i. e. local complications as listed on p. 126, articular symptoms and low serum albumen) is 32 (23.8 %). If we include the cases with hepatic symptoms, the number of cases with complications increases to 45 (33.3 %). The number of cases with complications among the 103 that were under observation for at least  $2\frac{1}{2}$  years is 38 (36.8 %) or, including cases with liver symptoms 47 (45.5 %). If hepatic symptoms are regarded as a complication, then 35 cases had 1 complication, 8 cases 2 complications, and 2 cases 3 complications.

#### *Treatment*

All the cases were treated in hospital, the majority of them several times over periods of several months. Most of them were nursed in bed for shorter or longer periods. (The material testifies to the advisability of individualizing hospital treatment and the keeping of the patient in bed.)

Cases dating from earlier years were as a rule treated with strict diet (a classical diet for patients with acute diarrhoe). In

more recent years there has been a marked tendency towards freer diet. Cases treated in recent years at Karolinska Sjukhuset and Kronprinsessan Lovisa's Children's Hospital have usually been allowed a varied, mostly normal, diet from which only the coarser vegetables have been excluded. The treatment yields better results with this freer diet. Not infrequently, however, we find a transient effect from a strict diet *at the onset* of the disease. But when it has passed into the chronic remittent stage, the patient's health shows no improvement ascribable to a strict diet; on the contrary, it frequently shows improvement when the diet is more liberal. Apparently it was often found necessary to prescribe a strict diet during acute bouts of illness, but even then the patients were frequently able to stand food surprisingly well (even if the evacuation is temporarily worsened by a coarser diet, it happens that the general condition is nevertheless improved).

103 cases were treated with sulphanilamide compounds during some period of the illness. 54 were treated with 1 drug, 24 with 2, 14 with 3, 8 with 4, 2 with 5 and 1 with 6. The most common drugs used and the results obtained will be found in Table 5. In addition, isolated cases were treated with salazotiazol, sulfadital, elkosine or prontosil. Moreover, during treatment the patients were subjected to the usual internal therapy [confinement to bed, sometimes diet, other remedies (see below)]. Only cases given a satisfactory dosage over a sufficient period (at least 7 days, *as a rule longer*) have been included in the table. Actually the doses and periods of treatment vary considerably. Even, however, if only those cases are included which received the max. dosage over a period of months, the conditions show no appreciable change. The best results seem to have been obtained with salazopyrine (82 cases) and the next best with phtalylsulfathiazole (13 cases) (Table 5). Frequently a patient showed no improvement after the first drug was administered, but seemed to benefit from some other. The usual dose of salazopyrine was 0.5 g 6 times in 24 hrs., although a number of smaller children were given 0.25 g 6 times in 24 hrs. Some cases received a dose of 1 gr  $\times$  6 for a briefer period. Particularly in Karolinska Sjuk-

*Table 5.*  
The immediate result of chemotherapy.

Result of treatment	Salazo-pyrine	Sulfa-thiazol	Sulfa-dimin	Sulfa-pyridine	Sulfitalyl	Sulfa-guanidine	Sulfa-digesine	Lucosil-enema
Number treated..	82	15	10	21	13	18	10	15
	%	%	%	%	%	%	%	%
Improved.....	63.4	33.3	50	47.6	61.5	50	40	60
Possibly improved	15.8	20	20	14.3	7.7	16.7	10	6.7
Unimproved .....	20.8	46.7	30	38.1	30.8	33.3	50	33.3

huset the patients were given minor doses over long periods broken by short intervals. An instance of an apparently successful salazopyrine treatment is given below:

*Case 58.* Kronprinsessan Lovisa's Children's Hospital No. 343/43. Girl. Birthweight, delivery, feeding and development, normal. Acute attack at age of 4, with fever and bloody diarrhea; well after several weeks. 2 years later, whooping cough and relapse with frequent loose, bloody stools. Patient grew thin, but was well again after several months. After c. 1 1/2 yrs another relapse lasting 5 mos. Subsequent improvement for 6. Then admitted to children's hospital. Emaciated, but no anemia; rectoscopy showed ulcers. Treatment: confinement to bed, mixed diet and salazopyrine (0.25 g. 6 times per diem, later 4 times). *Immediate improvement, deterioration when drug was withheld and improvement when again administered.* Discharged with health considerably improved, increase in weight; general condition better, with 1 semi-solid evacuation per diem. Subsequently *minor dose of salazopyrine* at home. Subsequently under observation 2 1/2 years; *no serious relapse.* When attacked by infections in upper respiratory tract frequent evacuations. Not invalidated; went to school. Follow-up examination: general condition good, normal evacuation.

Complications associated with salazopyrine treatment were as follows:

Sickness (vomiting and headache).....	6 cases
Skin eruptions and fever.....	4 »
Leucopenia.....	1 »
Purpura and fever.....	1 »
Total	12 cases (15 %)

None of the complications was severe and in several cases the treatment could be continued with the dosage reduced. As table 5 shows other compounds were used less frequently. After sulfathiazol 1 patient had leucopenia and another exanthem. One patient showed a rash after having taken sulfaguanidine while another had the same symptom after receiving prontosil.

The treatment with sulfanilamide compounds was far more successfull in the earlier stages than later on. Only 44 were treated during the first year of illness and very few during the first months. Only 18 of these 44 were under observation for at least  $2\frac{1}{2}$  years after treatment. (See »Discussion and conclusions».)

*Penicillin i. m.* was used in 7 cases, and *streptomycin i. m.* in 1 case and *per os* in 1 case; in none of these were the results striking.

The *symptomatic treatment* was of many different kinds. Frequently several methods were employed simultaneously, making it difficult to gauge the effect of each method separately. One common form of treatment was *enemas*. The most common enema solutions were collargol in a 1/8—1 % solution, 1/2 % alum and lucosil (about 2 % in a 4 % solution of agar-agar). The results are difficult to judge but were apparently satisfactory (especially with an agar-agar-lucosil solution).

*Iron*, usually in fairly large doses, was administered to 58 cases over a lengthy period. 51 of these cases showed improvement. In some cases the patient could not stand the first iron drug tried but improved when some other was administered. 31 cases were given at least one *blood transfusion*. In all these cases except 2 there was improvement in the general condition and in the blood values, though generally it was only temporary. 8 cases were treated with *vaccine* prepared from enterococci isolated from the patient's own intestine. 5 of these improved (post or propter). Several patients seem to have derived benefit from spasmolytica, especially when in the acute stages. The majority were occasionally given extra *vitamins* orally or parenterally. The effect is difficult to gauge. In 1 case (No. 66) large doses of vitamin D<sub>1</sub> were administered, and resulted in a transient

intoxication accompanied by, among other things ecg changes. Treatment of the complications was usually symptomatic. The good effect of heparin on thrombosis and the basic disease in Cases 70 o. 74 is noteworthy.

Some patients received *psychic treatment*, apparently with good results (Case 127 was published by Gunnarsson in NMT 1948). A few patients derived benefit from a *change of environment*.

Only 1 case received *surgical treatment* in connection with the basic disease: namely case 108 in which after 13 years of the disease, cecostomy was performed. The patient became worse after the operation and the cecostomy was closed 2 years later.

#### *Follow-up Examinations*

All cases except 3 underwent follow-up examination i. e. they were followed up until the investigation was concluded. The aforementioned 3 were followed up, respectively, 5 years, 3/4 and 1/4 of a year after the onset of the disease. Out of the 131 cases subjected to follow-up-examination, 10 died during the period of observation. Of these 10 fatal cases, the cause of death in 5 (= Group I: Nos. 14, 18, 51, 98 and 117) was u. c. or direct complications thereof. In 3 cases (= Group II: Nos. 15, 25 and 71) the cause of death was infectious diseases while more or less affected by u. c. In 2 cases (Group III: Nos. 64 and 116) the cause of death was hepatic cirrhosis.

In most respects there is no difference between these 3 groups. The age at which the disease set in in Group I (4, 5, 10, 11 and  $12\frac{1}{2}$  years respectively) is as a rule higher than in Group II (5, 1 and 2 years). The duration of the disease is also longer in Group I than in Group II (the averages being 6.5 (3—11 years) as opposed to 1.9 years ( $1\frac{1}{2}$ — $4\frac{1}{2}$  years)). In regard to common symptoms, all 3 cases in group II showed delayed growth during the course of the disease, but only 1 case in group I. All the cases in group II, except one, had complications; 5 had 2 complications. The most common complications were: aphthous stomatitis, thrombosis of the leg, arthritis, hepatic cirrhosis and skin eruptions.

Of the 6 cases examined rectoscopically, 4 were found to have ulcerous mucous membrane. Of the 7 cases who underwent X-ray examination, 5 showed changes in the entire colon and 2 no changes in the colon, but in the 2 latter the examination was made at an early stage of the disease. In 1 case not examined with X-ray the post mortem showed changes in the rectum, the entire colon and the terminal ileac loop.

All the cases showed severe anemia; in 6 the Hb was 50 % or less. S. r. in the 8 cases in which it was determined showed a moderate increase (34—48 mm) in 3 cases, a heavy increase (54—80) in 4 cases and in 1 case it was 10 mm.

Hospital treatment had been commenced at different times as shown in the following table. The figures within brackets denote the number of cases treated with chemotherapy. (Altogether 7 cases were thus treated.)

Length of time between onset of Disease and commencement of treatment

Nuber of cases

2 mos or less.....	4 (1)
4—6 mos.....	3 (1)
3—4 years.....	2 (3)
5—6 years.....	1 (2)

That is to say, in 2 cases chemotherapy was initiated (after 4 and 5 years respectively) at a date subsequent to the other hospital treatment.

In all cases the hospital treatment was successful at the outset. 6 out of 7 treated with chemotherapy improved considerably both upon first receiving treatment and upon subsequent exacerbation. 2 cases were treated with 5 different drugs, 1 with 3 different drugs, 2 with 2 and 2 with only 1 drug. 5 cases were treated with salazopyrine, in 1 case this treatment was started after about 1 month's illness, but in the other cases not until several years after the disease set in (3, 4, 5 and 6 years, respectively).

In 6 cases a post mortem examination was performed: 4 out of the 5 cases in Group I, and both cases in Group III). In 3 of these cases perforation of the colon was found in the peritoneum in conjunction with peritonitis. In Case 117, cancer of the colon

with hepatic metastasis was established. Case 64 revealed hepatic cirrhosis and general polyposis in the colon and Case 116 hepatic cirrhosis, while the colon was stated to be macroscopically normal.

Out of the other 121 cases followed up the author himself has examined 44. The examination included tracing the anamnesis from the mother and/or the patient, determining the patient's height and weight and a complete somatic examination. In the majority of cases a rectoscopical examination was also undertaken, and in some cases an X-ray examination of the colon. In all cases an examination was made of the blood, sedimentation rate and the feces (including bacteriological culture). — At the time of the follow-up 36 cases were under hospital treatment, and some of these were examined by the author, while in the other cases a copy was taken of the medical history record.

From the remaining 44 cases, data were obtained by means of a questionnaire. The particulars given therein were supplemented in a number of cases by information from the doctors or hospitals that had treated the patient.

By this means the patient's condition could be followed from the onset of the disease to the follow-up examination (Diagram I). The markedly remittent and intermittent course of the disease will be seen from the diagrams (for its course see also above). In the majority of cases periods of improvement alternated with relapses. The length of the periods varied, though as a rule they were less than 2 years; i. e., if a patient was free from symptoms for 2 years, he seldom had a relapse (Group A in Table 6 etc.). Under Group B are included patients who were free of symptoms at the follow-up but had not yet been free from symptoms for 2 years, and patients who at the time of the follow-up exhibited symptoms of u. c. without being invalidated. The patients in this group went to school or carried on their work and even in other respects lived a more or less normal life. Many regarded themselves as in good health but upon contracting infections in the upper respiratory tract had frequent loose evacuations. Among Group C are numbered those patients who at the time of the follow-up were actively ill and invalidated.

Table 6.

The prognosis for all cases observed at least  $2\frac{1}{2}$  years.

Follow up condition	Cases obs. at least $2\frac{1}{2}$ yrs	
	Number	%
A		
Free from symptoms at least 2 yrs	31	30.1
B		
Unwell but not invalidated (see text)	52	50.5
C		
Invalidated .....	10	9.7
D		
Died.....	10 <sup>1</sup>	9.7
Total	103	100.0

<sup>1</sup> 2 cases died within the first 2 years of disease.

Table 7.

Patients' condition in relation to duration of disease.

Condition	Years after onset of disease					
	3	6	9	12	15	18
A						
Free from symptoms at least 2 yrs.....	6	11	12	9	5	3
B + C						
With symptoms (see text) ....	92	56	28	13	6	3
D						
Died.....	3	4	2	1	0	0
(Died tot.) .....	(3)	(7)	(9)	(10)	(10)	(10)

The majority of them were hospital cases. In view of the course of the disease and the requirement of 2 years' freedom from symptoms before a patient is regarded as cured, only those cases observed at least  $2\frac{1}{2}$  years after first falling ill have been included in Table 6 and diagram I (all cases who died being included).

### Discussion and Conclusions

In spite of the comparative completeness of the data, the author has not found any common constitutional features in these patients such as could explain how the disease arose. The children included were as a rule from middle-class families, were born at the normal time and were breast-fed. Generally speaking, their development was normal and previously they had normal evacuations. The material comprises a relatively larger number of boys (58 %) than girls in contrast to other comparable materials, where the sexes are equally divided. A relatively large number of cases may possibly have had infections of the upper respiratory tract with striking frequency even before falling ill (see above). In spite of the fact that a substantial portion of the cases were never closely studied with regard to psychical environment, it was found to be unsatisfactory in 25 cases. Moreover, the above-mentioned instances of psychical causes of deterioration in health and of the good effect of psychiatric treatment point to the presence of psychosomatic factors in the disease. This substantiates modern views (SULLIVAN, GUNNARSSON and others). Continued inquiry into the psychological environment and constitution of the cases seems to be indicated.

The insidious onset of the disease, its prolonged, remittent course and the negative results of repeated feces cultures exclude the possibility that bacillary dysentery may play a part in its etiology (cf. the view of HURST and others). In his material the author, like several earlier investigators (among others SVARTZ and BARGEN), has observed a relative increase in the cocci in the intestinal flora at the expense of the coli-bacteria. Moreover, the author has proved that there is a relative increase in

the hemolytic types of bacterium coli in proportion to the an-hemolytic types (Table 4). When forming an opinion of these findings we must take into account the change in the environment of the intestinal flora. The cocci are normally to be found in the upper part of the large intestine and the lower part of the small intestine. They thrive in the liquid, blood-containing culture medium which the bowel-content in u. c. constitute. A relative increase of them in the feces tests *may be* secondary, like their invasion of the mucous membranes of the rectum and the colon. The primary changes (if any) in the intestinal flora are still unknown. It is questionable, however, whether the cocci and the hemolytic colon bacilli are capable of playing a secondary part in furthering the development of the disease.

In some cases a relative increase of the cocci (compared with the colon bacilli) was observed during chemotherapy. This has been proved earlier. It can be due to the fact that *B. coli* usually is more sensitive to sulfanilamides than are enterococci. From this it seems that these remedies do not give results through a suppression of the enterococci.

The author's cases indicate a greater frequency of injuries to the liver (see below) than has been found in other quarters. In a number of cases the injury to the liver would appear to have preceded the disease. Future investigations will have to show whether the liver is a causal factor in the inception and development of the disease and if so in what manner.

It has been shown in Fig. I and in the above discussion that the disease has become more frequent in Stockholm of late years. The reason for this is unknown. At any rate, there has been no change for the worse in hygiene or in food conditions. It may be argued that overcrowding has increased, leading probably to friction in family life and other ills due to environment. If the view that the disease has a psychosomatic character is correct, this may be a contributory factor. It has been shown above (Fig. 2) that the frequency maximum for children contracting the disease lies between the ages of 2 and 6, whereas in the material collected by JACKMAN, BARGEN and HELMHOLZ this maximum approaches the material's upper limit. One hypo-

thesis put forward in explanation of this is the difficulty of bringing up children between the ages of 2 and 4 (the first »defiant» age).

The majority of the cases in our material have, like those in other investigations, fallen ill without connection with any other disease. On the other hand, this material differs from the large American series in the manner in which the patients fell ill. Here, as in the case of adults in Scandinavia (SVARTZ, MOLTKE), the primary chronic type predominates. The acute cases are few and not pronounced, nor do they differ from the rest in regard to the prognosis (cf. BARGEN, HELMHOLZ and JACKMAN). — As to early symptoms, the group that has blood on otherwise normal feces (14 in this material) as the only first symptom has hitherto not been adequately observed. This manner of falling ill occurs in cases with isolated proctitis, some of which heal completely before the disease has spread to the upper portions of the intestine.

As in other series, the most common symptoms have been frequent loose, bloody evacuations and emaciation. The latter symptom has been proportional to the degree of severity and the distribution of the disease. Delayed growth, which is very rare in other material, has occurred in 8 cases in which the disease was severe and widespread. As in earlier material, the anemia was as a rule hypochromic. Our material, like that of POLLARD and his colleagues, shows that the hemoglobin values are closely correlated with the degree of severity of the disease (and loss of weight) and also with the prognosis, but bear less relation to its distribution (Table 3). The sedimentation rate shows relatively little relation to these factors.<sup>1</sup> This material refutes the suggestion (MOLTKE) that a sedimentation rate of over 20 mm/1 hr. indicates a bad prognosis.

Rectoscopy has proved to be useful. Although it is frequently possible to make the diagnosis without this examination, it affords rapid diagnosis and makes it easy to follow the development of the disease. It has proved easy to carry out and as a rule, not very troublesome to the patient. It has been the author's experience, that preparation in the form of enemas and laxatives

<sup>1</sup> But is probably more influenced by factors as infections of upper respiratory tract and complications than is the hemoglobin value.

should be reduced to a minimum. The most common changes in the rectal mucous membrane have been redness, swelling, granulation, and also increased vulnerability. The presence of an ulcer need not necessarily be demonstrated in order to make the diagnosis. (For several reasons the groups on page 121 are not essential.)

The X-ray examination of the colon has also proved useful in this material in determining the spread of the disease. The entire colon was attacked in 66 %. (One must, however, remember that most cases were not followed with X-ray during the whole period of observation.) The most common change was sparse or suspended hastration and an irregular mucous membrane relief. In 9 cases the disease also attacked the lowest part of the ileum; similar cases have been described by HELMHOLZ. The changes resembled those in the colon. These cases were relatively seriously affected but did not show celiac type of disease as GLANZMANN and ASCH have maintained. In a number of cases the X-ray examination has brought to light serious changes (lead-pipe colon and the like) even when the patient has been clinically healthy. 3/4 of the cases examined with a test breakfast have shown normal acid values, a fact that tallies with more recent examinations. The examinations of feces has confirmed earlier investigations. In not a single case have signs been found of a poor digestion. In a relatively large number of cases an abundance of iodophile bacteria, chlostridiae and substance has been proved. The bacteriological examinations have already been discussed above.

In this, as in most of the earlier material, the course of the disease has been markedly remittent or intermittent (Diag. I). The most common cause of relapse has been infections of the upper respiratory tract, this probably being more pronounced than in BARGEN, HELMHOLZ and JACKMAN's material (climatic dissimilarities?). The usual course has been as follows; the patients gradually fell ill and by degrees became to some extent invalidated subsequently there was some improvement interrupted by relapses, but gradually no further invalidization and symptoms mainly in the event of infections of the upper respiratory tract.

Mention has been made above of the difficulty of deciding what symptoms during the period of sickness are to be regarded as complications. The material records far more cases of hepatic injuries (15.9 %) than earlier material. The probability has been advanced above (p. 129), supported by quotations from literature, that these injuries are to be regarded as complications. The cause of injury to the liver may be the poisons conveyed to it from the intestine or the lack of albumen that arises through the loss in the feces, as TUMEN, MONAGHAN and JOBE have maintained. Further inquiries into the part played by the liver in the development of the disease seem to be indicated, especially as cases having liver symptoms have a worse prognosis than the others (Table 2).

Joint symptoms occur in this material more frequently than in most other materials (12 %). Only 9 cases had objective articular symptoms (of which 2 may possibly have had independent polyarthritis), but this frequency is higher than that in adults in Scandinavia, according to SVARTZ. The course tallies with earlier data. Of the other complications, thrombosis has occurred more often than in other larger materials (6 cases). This is particularly interesting, as that symptom generally is unusual in children. Local complications are relatively uncommon, especially if compared with the conditions in adults in American materials. 1 case of cancer in the colon, 1 case of polyposis in the colon and 2 cases of anal eczema were the most important local complications; these have been previously described as occurring in children. The figures with regard to the number of complicated cases (p. .) are somewhat lower than in JACKMAN's, BARGEN's and HELMHOLZ' material, and even lower than in most other materials.

131 out of 134 cases have been followed up. 10 died during the period of observation. This is a lower mortality rate than in most other comparable materials. 5 cases died of u. c. or its direct complications, 3 of infections of the upper respiratory tract more or less concomitant with an attack of u. c., and 2 of hepatic cirrhosis. The age at which the patients fell ill and the duration of the disease vary widely — in contrast to the other materi-

als, in which most of the cases of death occurred among infants and the duration of the illness was as a rule less than one year. In the cases that proved fatal the disease attacked the entire colon and caused severe anemia. Complications were relatively frequent, symptoms from the liver and thrombosis being the most important. In these cases chemotherapy has as a rule been used at a late stage but nevertheless has initially led to improvement. See also the summary on p. 134—135.

The result of the follow-up examinations is shown in Diagram I and Table 6 and 7.

Diag. I and Tabl. 7 supports the view of JACKMAN, BARGEN and HELMHOLZ that a patient who has been free from symptoms for 2 years seldom has a relapse. It will be seen from Table 6 and 7 that the prognosis for this material is serious but better than that for materials of American children. There are no comparable figures for adults in Scandinavia, but to judge from MOLTKE's material their prognosis is also worse than that for this material. The fact that the prognosis is better for children than for adults is in keeping with the common experience that children's capacity for recovering from chronic disease is generally greater than that of adults. It may also be gathered from Diagram I and Table 7 that the prognosis as a rule becomes better the longer the patient is under observation, which contradicts the above-quoted experience of, among others, PAULSON. The time of complete recovery does not as a rule coincide with the arrival of puberty (Diagram I).

The chief signs of a bad prognosis are progressive anemia (Table 3), the spreading of the disease over the entire colon (Table 2) and the appearance of hepatic symptoms (Table 2) whereas absence of serious anemia is a good sign. The prognosis is also poorer for cases with delayed growth and high temperature. Neither an acute attack of the disease nor falling ill at an early age worsen the prognosis in this material, though they have been proved to do so in other materials. Cases with allergy symptoms or heredity do not differ from the rest in the matter of prognosis. Cases that have suffered from a bad psychological environment and cases showing symptoms of neurolability

apparently have a somewhat worse prognosis than the rest (not definitely established).

As a rule differential diagnosis has not given rise to any difficulties in this material. The most important differential diagnosis is likely to be concerned with milder forms of diarrhoeic diseases in children. If a case is followed with examinations of feces and blood as well as rectoscopy and, possibly, X-ray examination, it should generally be possible fairly quickly to distinguish this milder disease from u. c. Bacillary dysentery and infections by salmonella group may generally be excluded by following the course of the disease and by making repeated cultures of feces. Tuberculosis, primary polyposis and cancer are hardly likely to cause differential diagnostic difficulties in childhood.

With regard to treatment our material confirms the modern idea that hospital treatment, confinement to bed and diet must be entirely individual matters. Children suffering from u. c. should as far as possible be treated as if they were healthy. The majority can easily stand a light varied diet. Severe dietary restrictions should be imposed for as brief periods as possible, as they impair the general state of health.

The results obtained from different forms of treatment are difficult to judge as, generally, several methods have been employed at the same time and the disease shows a great tendency to spontaneous improvement or deterioration.

All cases have temporarily got only some older forms of treatment (ex. hospital care, iron, bloodtransfusion, spasmolytics, enemas) and 31 had only some of these remedies and never got chemotherapeutics. Most cases showed improvement by these older remedies. Cases included in tabl. 5 (immediate results of chemotherapy) have simultaneously with chemotherapeutics had some forms of these other remedies as well. Thus the results cannot be attributed only to the sulfanilamides. If compared with the group that failed to receive such drugs it is obvious that chemotherapy has been of value and sometimes of striking value.

Salazopyrine (83 cases) is the best drug as shown earlier by SVARTZ. It shall be administered early in the disease in fairly

large dosage over at least 3 weeks (in general longer). Later on one ought to give smaller dosage, even in the convalescence (as recommended by SVARTZ). Phtalylsulfathiazol (sulftalyl) was only given to 13 patients, the results were not quite as good as with salazopyrine. (The results with lucosil-enemas cannot be compared with other results in tabl. 5 as cases thus treated generally were in a better condition at the instalment of treatment than the rest.)

If one sulfanilamide compound fail to give results one ought to try others.

As a rule chemotherapy had not so good effect on the development of the disease in the long run as might be supposed from the immediate results (see diagram I). These results were better in early stages of disease than later on. However, not even early chemotherapy could prevent relapses and progression of disease. But chemotherapy often had good effect even in relapses.

As, however, few patients had adequate chemotherapy early in the disease (and were later observed over a longer period) one cannot say anything definite on the role of such treatment for the long range prognosis. As stated above the literature has been scarce on the subject.

The earlier methods of treatment have justified themselves in this material also. Most cases improved after being given iron medicine and blood-transfusion, many derived benefit from enemas (especially agar lucosil enema as recommended by SVARTZ). The author has likewise found spasmolytics and extra vitamines to be useful in some cases.

Considering the psychosomatic factors psychical investigation and ev. treatment seem indicated in most longstanding cases.

### Summary

Following a survey of literature the author gives an account of a clinical and bacteriological investigation of 134 cases of ulcerative colitis (u. e.) in children, with a follow-up study. (Tabl. I.) The disease is found to have become more common in Stockholm in recent years. Some facts are presented showing

that psychic factors may be of importance in the development of the disease. The bacteriological examinations, which excluded *Salmonella* and *B. dysenteriae* demonstrated that the cocci and hemolytic types of colon bacilli are preponderant in the feces during acute stages (tabl. 4). These findings are discussed.

Most of the cases suffered insidious attacks. The most important symptom consisted in loose, frequent sanguineous evacuations attended by emaciation. The majority of cases were periodically subfebrile and had hypochromic anemia, leukocytosis and high sedimentation rate. Progressive anemia frequently implied a bad prognosis (Tabl. 3). Rectoscopy has shown changes at various stages from a swollen, granulated easily bleeding mucous membrane, to ulcers and scars. In about 2/3 X-ray-examination has shown changes in the entire colon and in 9 cases in the terminal part of ileum as well (tabl. 2).

131 cases have been followed up. The course of the disease was markedly remittent and intermittent (diagram I). A patient had to be free from symptoms at least for 2 years before the chance of a relapse was small. Complications arose in about 1/3. The most interesting of these involve injuries to the liver (21 cases) and thrombosis (6 cases). 10 patients died, 5 of them in progressive u. c. The prognosis (tabl. 2, 3, 6 and 7; diagram I) is serious but better than in most other materials. In many cases the disease has a tendency to cure itself in the long run (tabl. 7 and diagram I).

In regard to treatment it is emphasized that these patients should be allowed a rich, varied diet. Most cases showed improvement after bloodtransfusion and iron. 103 cases have received chemotherapy (Tabl. 5) the best results being obtained with salazopyrine. This should be given early in the disease in rather large doses over a long period. Psychic treatment is often indicated.

#### Résumé

Après un aperçu de la littérature, l'auteur donne un rapport d'un examen clinique, bactériologique et prognostique de 134 cas de recto-colite ulcéro-hémorragique (colites ulcérées) chez les enfants (Tabl. I). Cette maladie est devenue plus commune

à Stockholm ces dernières années. Certains faits indiquent que les facteurs psychiques peuvent jouer un rôle important dans le développement de la maladie. Les examens bactériologiques excluent les salmonellas et les bactéries de dysentérie comme cause et montrent que les bactéries entérocoques et les bacilles hémolytiques du côlon dominent durant la phase aiguë de la maladie (Tabl. 4). Ces découvertes sont discutées.

Dans la plupart des cas, la maladie avait un début insidieux. Les symptômes principaux étaient des évacuations sanguinolentes, purulentes et liquides, accompagnées d'amaigrissement. La plupart des cas étaient périodiquement subfibrillés et avaient: anémie hypochromique, leucocytose et degré de sédimentation élevé. L'anémie progressive indique fréquemment un mauvais pronostic (Tabl. 3). La rectoscopie a montré une membrane muqueuse enflée, rouge et saignant facilement, et dans quelques cas: ulcères et cicatrices. Dans environ les 2/3 des cas la radiographie du côlon a montré des altérations dans tout le côlon, dans 9 cas dans la dernière partie de l'iléon aussi (Tabl. 2).

131 patients ont été suivis. Le cours de la maladie avait un caractère manifestement rémittent et intermittent (diagram I). Un patient devait être sans symptômes au moins 2 ans avant que le risque d'une rechute fut faible. Il y a eu des complications chez 1/3 des cas. Les plus significatives étaient les symptômes du foie (21 cas) les trombos (6 cas). 10 patients sont morts, dont 5 d'une rectocolite ulcéro-hémorragique progressive. Le pronostic (Tabl. 2, 3, 6 et 7, diagram I) est grave mais meilleur que pour la plupart des autres maladies. Dans bien des cas la maladie a tendance à guérir d'elle même à la longue (Tabl. 7 et diagram I).

Au sujet du traitement, on insiste sur la nécessité que ces cas reçoivent une alimentation riche et variée. La plupart sont améliorés par le fer et la transfusion du sang. 103 cas ont eu un traitement de chimiothérapie. Le meilleur résultat a été obtenu par la salazopyrine qui doit être administrée au début de la maladie à doses relativement fortes et durant une longue période de temps. Un traitement psychique est souvent indiqué.

### Zusammenfassung

An Hand einer Literaturübersicht gibt der Autor einen Bericht über klinische, bakteriologische und prognostische Untersuchungen von 134 Fällen von Colitis ulcerosa bei Kindern (Tabl. 1). Diese Krankheit ist in den letzten Jahren in Stockholm häufiger geworden. Es scheint festzustehen, dass psychische Faktoren beim Krankheitsverlauf von Bedeutung sind.

Die bakteriologischen Untersuchungen, welche Salmonella und B. dysenteriae ausschliessen, zeigten, dass die Kokken und haemolytischen Typen der Colon-bacillen in den Faeces während des akuten Stadiums vorwiegen (Tabl. 4). Diese Befunde werden besprochen. Das wichtigste Symptom besteht in dünnen, oft blutigen Entleerungen, begleitet von Abmagerung. Die meisten Fälle waren periodenweise subfebril und hatten hypochrome Anämie, Leukocytose und hohe Senkungsreaktion. Progressive Anämie führte zu schlechter Prognose. (Tabl. 3.) Die Rektoskopie zeigte Veränderungen verschiedenen Grades, von geschwollener, granulierter schmerzlos blutender Schleimhaut bis zu Geschwüren und Narben. In ca 2/3 der Röntgenuntersuchungen zeigten sich Veränderungen im ganzen Colon und in 9 Fällen auch im Endteil des Ileums (Tabl. 2).

131 Fälle wurden verfolgt. Der Krankheitsverlauf war ausgesprochen remittierend und intermittierend (Diagr. I). Ein Patient musste mindestens 2 Jahre symptomfrei sein, bevor die Neigung zu einem Recidiv gering war. Komplikationen gab es in 1/3. Davon verdiensten das grösste Interesse Leberschäden (21 Fälle) und Thrombose (6 Fälle). 10 Patienten starben, 5 davon an progressiver Colitis ulcerosa. Die Prognose (Tabl. 2, 3, 6, u. 7) ist ernst, aber besser als in dem meisten andern Material. In vielen Fällen hat die Krankheit eine Tendenz zur Selbstheilung nach langem Verlauf (Tabl. 7 u. Diagr. I).

In Bezug auf die Behandlung wird betont, dass diesen Patienten eine reichliche, abwechslungsreiche Diät erlaubt werden soll. Die meisten Fälle zeigen Verbesserung nach Bluttransfusion und Eisen. 103 Fälle bekamen Chemotherapie (Tabl. 5), die besten Resultate erhielt man durch Salazopyrin. Dieses soll

vom Beginn der Krankheit in ziemlich grossen Dosen lange Zeit hindurch gegeben werden. — Oft ist psychische Behandlung angezeigt.

#### Resumen

Después de una exposición de la literatura profesional, el autor informa sobre un examen clínico, bacteriológico y pronóstico de 134 casos de niños con colitis ulcerativa (cuadro 1). Durante los últimos años esta enfermedad ha sido muy común en Estocolmo. Algunos hechos indican trazos psicosomáticos en la sintomatología. Los cultivos bacteriológicos excluyeron las bacterias de *Salmonella* y las bacterias disentéricas como causa y demostraron que, en los estados agudos de la enfermedad, dominaban bacterias parecidas a enterococos y colibacilos hemolíticos (Cuadro 4). Se discutieron estos hallazgos.

La mayoría de los enfermos enfermaron lentamente. El síntoma más corriente era evacuación sangrante, purulenta y generalmente suelta, acompañada de enfraquecimiento. La mayoría de los casos eran temporalmente subfebris y tenían anemia hipocróma, leucocitos y alto S.R. La anemia progresiva indicaba un mal pronóstico (Cuadro 3). Una rectoscopía mostró una mucosa hinchada, roja, ligeramente hemorrágica y en algunos casos úlcera y cicatriz. Los roentgenogramas mostraron, en aproximadamente dos terceras partes de los casos, alteraciones en todo el colon, y en 9 casos también en el lazo terminal del ileón (Cuadro 2).

Se han efectuado exámenes posteriores de 131 enfermos. La enfermedad tenía una marcha pronunciadamente intermitente y remitente (Diagrama I). Sólo en el caso en que el enfermo no había tenido síntomas durante 2 años, el peligro de recidiva era pequeño. Se presentaron complicaciones en aproximadamente una tercera parte de los casos; las más importantes eran lesiones del hígado (21 casos) y trombosis (6 casos). 10 enfermos murieron y de ellos la mitad de colitis ulcerativa progresiva. El pronóstico (Cuadros 2, 3, 6 y 7, Diagrama I) es serio, pero mejor que el de la mayoría del otro material. La enfermedad en muchos

casos tiene a la larga una tendencia a curarse (Cuadro 7 y Diagrama I).

Por lo que se refiere al tratamiento, se sostiene que estos enfermos deben seguir una dieta abundante y perfecta. La mayoría de los enfermos mejoran por medio de hierro y transfusión de sangre. 103 casos han recibido quimioterapia (Cuadro 5). El mejor resultado se ha obtenido con «salazopyrina», que se debe dar al principio de la enfermedad en dosis bastante grandes durante largo tiempo. Un tratamiento psíquico es muchas veces conveniente.

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FROM THE PEDIATRIC CLINIC OF KAROLINSKA INSTITUTET (CHIEF: PROFESSOR A. LICHTENSTEIN) AND THE DEPARTMENT OF CHILD SURGERY (CHIEF: PH. SANDBLOM, M. D.) AT KRONPRINSESSAN LOVISA'S CHILDREN'S HOSPITAL, STOCKHOLM.

## **Electroencephalography Following Head Injuries in Children**

by

**KARL-AXEL MELIN**

When a patient with a head injury is admitted to a hospital department, it is often difficult to determine the nature and extent of the injury. If, for example, it is a case of concussion of the brain, knowledge of the immediate course at and directly after the actual accident plays an important part in determination of the nature and degree of severity of the injury. Yet often, particularly where children are concerned, the sequence of events when the injury occurred remains obscure. Perhaps there was no adult witness. The child's playmates' descriptions of what happened are widely divergent. Information as to whether or not there was unconsciousness is frequently vague. Many times the injured child has been able to return home himself after the accident and the parents have not brought him to the hospital until vomiting, giddiness, or general deterioration in condition have set in after some hours.

Later on, when it has become necessary to form an opinion concerning the course of healing in concussion, we have hitherto had to be guided for the most part by the purely clinical picture, something which in a large number of children's cases has meant that it was very difficult to arrive at any clear idea. Many of the subjective disturbances which an adult can report and which afford valuable aid when the doctor wishes to visualize the situation are either absent in children or at any rate do not appear very distinctly.

Since about 1940 a number of investigations have shown that electroencephalographic examinations are of value both in esti-

mating the extent of an injury following cerebral trauma and in following the subsequent course of healing. In 1941 WILLIAMS and DENNY-BROWN reported on some basic experimental attempts on animals. They studied EEGs of cats subjected to local and general cerebral trauma under light anesthesia. They found that blows resulting in concussion always caused an instantaneous and generalized diminution in the cerebral electrical activity as recorded in the EEG. This diminution persisted after reflex activity returned. There was then a delayed appearance of abnormally slow waves similar to those seen after concussion in man. The cerebral electrical changes caused by local trauma were limited to the injured area, but they were similar to the generalized changes seen in concussion. According to the authors' opinion, reversible changes caused by local and general cerebral trauma are identical and concussion is the direct result of mechanical violence to cerebral cells.

In 1944 and 1945 Dow, ULETT, and RAAF reported on examinations of man following injury. They carried out their investigations at Kaiser's Oregon Shipbuilding Corporation, at that time employing approximately 33 000 persons. In a first aid station they were able to register, many times within 15—30 minutes after the accident, EEGs from 197 patients who had sustained mild injury. If mild cerebral trauma produced changes in the EEG the abnormality disappeared within a period of minutes in the vast majority of cases. Patients who gave a history of amnesia following the cerebral trauma, but were clear mentally when the EEG was taken a short time later, showed only a slight increase in the percentage of abnormal records as compared with the control series. If there was an impairment of consciousness of any degree at the time when the EEG was taken, abnormality of the EEG was the rule. In the patients with abnormal EEGs the average velocity of the striking object or of the falling head at the time of impact was greater than the velocity necessary to produce concussion in experimental animals. In the patients with normal or borderline EEGs it was less than the velocity necessary to produce concussion in animals.

Lastly, in 1947 a comparative histological and electroencepha-

lographic investigation by ZIMMERMAN and PUTNAM afforded further confirmation of the connection between concussion of the brain and EEG abnormalities following head injuries. Their investigations were made on cats. With a special traumatizing instrument they applied graded force to the exposed brain during simultaneous EEG registration both from the traumatized side of the head and the other side. A second record was made 4 days later. The animal was killed immediately after the end of the last recording and the brain examined histologically. The experiments showed a direct relation between the amount and degree of cortical cell change and the degree of electroencephalographic change following trauma. When a minimal force was applied, no electroencephalographic changes occurred. Histological examinations, however, revealed minimal changes scattered throughout all cortical layers. When the force was increased above a distinct level the amount of electrical and cortical change was a function of the intensity and duration of the force applied. The authors' histological findings correspond to those of RONCALI described as early as 1898. He subjected the cerebral cortex of dogs to compression and afterwards was able to establish the presence of typical histological cell changes in all the cortical layers.

The connection between acute head injury and electroencephalographic changes shown by these authors, among others, has been applied in a number of purely clinical examinations. In 1945 JASPER, KERSHMAN, and ELVIDGE gave a good summary of these questions, basing their views partly on cases they had observed themselves. They consider the principal characteristics of the EEG changes after head injury to be «a) irregularities, reduction, or complete disappearance of normal cortical rhythms, b) appearance of slow waves at frequencies from less than 1—7 per second, and c) production of excitatory changes in the form of rapid rhythms, spikes, and sharp waves». Studies correlating clinical data and EEG findings convinced the authors that ratings of cerebral damage after head injury based upon clinical history and general clinical examination correlate fairly well with the severity of the EEG changes within the first 10 days

following the injury. After mild injuries and during recovery the EEG is frequently a more sensitive measure of cerebral damage than is the routine clinical estimate alone. Patients with abnormal neurological signs immediately after injury or with skull fractures, increased intracranial pressure, or blood in the cerebrospinal fluid are more likely to show severe and persistent EEG changes. EEGs taken a few hours after injury are, if changed, of less importance than records taken the following days, however. The latter provide a more reliable picture of the residual damage to the cerebral tissue. The authors consider the EEG to be a useful additional guide to the management of convalescence following head injury, but it cannot be used alone, since persistent EEG abnormality does not preclude return to active duty or productive work. They emphasize the fact that the EEG is not a substitute for careful clinical study of the patient, but that in conjunction with it, it makes a valuable individual contribution.

The last observation above has also been emphasized by, among others, PUECH, LERIQUE-KOECHLIN, and LERIQUE and later by PUECH, FISCHGOLD, VERDEAUX and BRUN. These authors point out that a recent head injury may exist with a normal or nearly normal EEG, and that recent skull fracture, concussion, or even laceration of the brain may cause only slight abnormalities. Hence a normal EEG cannot definitely rule out post-traumatic cerebral lesions. In such cases repeated recordings from many areas guarantee better results. Persistently abnormal EEG patterns following craniocerebral injuries are, on the other hand, a grave prognostical sign, in the long run indicative of a possible post-traumatic convulsive state.

I have not been able to find any summarizing investigation on the subject of the EEG picture in children with acute head injuries. Individual authors mention the fact that children show greater changes than adults, however. Thus PUECH and his co-workers demonstrate this and add that the irregular rhythms found in, for example, epileptic children are also found here. JASPER, KERSHMAN, and ELVIDGE conclude that apparently comparable trauma produce more profound EEG changes in

the heads of younger patients. They speculate on the possible cause of this and stress the fact that the cortical potentials are less stable in younger people. According to LIBERSON and STRAUSS, children react more quickly and in a more labile manner to metabolic disturbances. JASPER and his co-workers now think that they may also be more sensitive to different physical stimuli. Another possibility is that the skull is more rigid in older people and therefore offers more protection. In my own opinion the markedly irregular rhythm particularly in younger children is extremely significant. It probably has something to do with the development of the brain, particularly as regards the interneuronal connections, which are not completely formed until relatively late.

In order to investigate the special problems connected with EEG registration after acute head injury in children, all such patients admitted to the Department of Child Surgery at Kronprinsessan Lovisa's Children's Hospital were subjected to repeated electroencephalographic examinations. Up to the present 134 children between the ages 0—13 have been examined (Table I). Their injuries have been classified in 4 groups marked 1—4. Group 1 includes cases in which the head was exposed to a trauma of some kind, but one which failed to give rise to any clinical symptoms worthy of mention. Group 2 includes the cases in which there was momentary loss of consciousness, a slightly dazed condition, and vomiting or the like when the accident occurred or immediately thereafter. Group 3 includes the cases in which loss of consciousness lasted longer or the general effects were more marked. Group 4, finally, includes the severe cases in which loss of consciousness, a dazed condition, or pronounced ill effects lasted 12 hours or more. In addition there are a number of cases in which our knowledge of the nature of the trauma and the immediate sequence of events was so slight that classification could not be attempted. The electroencephalographic records have been graded in Groups 0 for normal EEGs and +, ++, and +++ for records with pathological changes, depending on the degree of change shown.

Of the 134 cases examined, 72, i.e. more than half, were

Table I.

Total number of cases .....	134
Examined within 24 hours after injury .....	72
♂      ♀      48      ♂      ♀      ♀      .....	82
♂      ♀      72      ♂      ♀      ♀      .....	99
♂      ♀      96      ♂      ♀      ♀      .....	117

## Age groups.

Group of Injury	0—2 Years	2—5 Years	5—10 Years	10—13 Years	Total Number
1	9	3	5	1	18
2	7	26	26	5	64
3	1	6	18	2	27
4	1	4	1	—	6
?	—	6	12	1	19
Total Number	18	45	62	9	134

admitted for examination less than 24 hours after the injury occurred. One hundred and seventeen children were examined for the first time within 4 days after the injury (Table I). Insofar as possible, the patients were examined thereafter every 2—4 days during their stay in the hospital and subsequently at weekly intervals until their EEGs were normal or practically normal. All the examinations were carried out with the aid of a 6-channel Grass electroencephalograph, Model III. I made routine use of silverplate electrodes attached with collodion, 8 of which were placed on the crown and 2 on the ear lobes, the latter acting as »indifferent electrodes». Upon the appearance or suspicion of focal findings extra electrodes were applied to the extent required. Both unipolar and bipolar leads were used, and all the electrodes were used for both lead methods.

The following problems were then taken up for consideration.

1. To what extent had EEG changes occurred in the different groups of injuries?
2. To what extent could a connection be observed between the nature of the injury and the EEG findings?

3. To what extent had the EEG changes observed disappeared again, and how did this disappearance compare with the clinical course?

4. What pathological changes had occurred within the electroencephalographic records, and to what extent were these localized to a particular area?

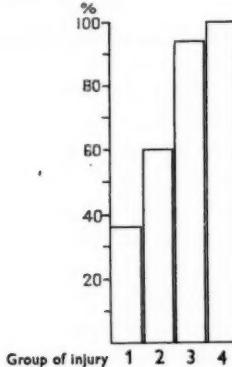


Fig. 1. Percentage of pathological EEG changes in different groups of injuries of 59 patients examined within 24 hours after injury.

To determine the extent to which pathological EEG changes had occurred in the different classes of injuries, the examination results for the 59 patients who were examined within 24 hours after injury and the circumstances of whose accidents were known were collected and compared. Thus the injury class or group of each could be definitely determined. I found (Fig. 1) that all groups of these patients showed EEG changes, but with increasing frequency, so that the majority of pathological findings fell in the groups with the most severely injured.

The connection between the nature of the injury and the degree of the EEG findings was investigated among the 117 patients examined within 96 hours after the injury took place (Fig. 2). The majority of normal electroencephalograms fell within the group of the least seriously injured. In the groups including the more seriously injured, pathological EEG changes

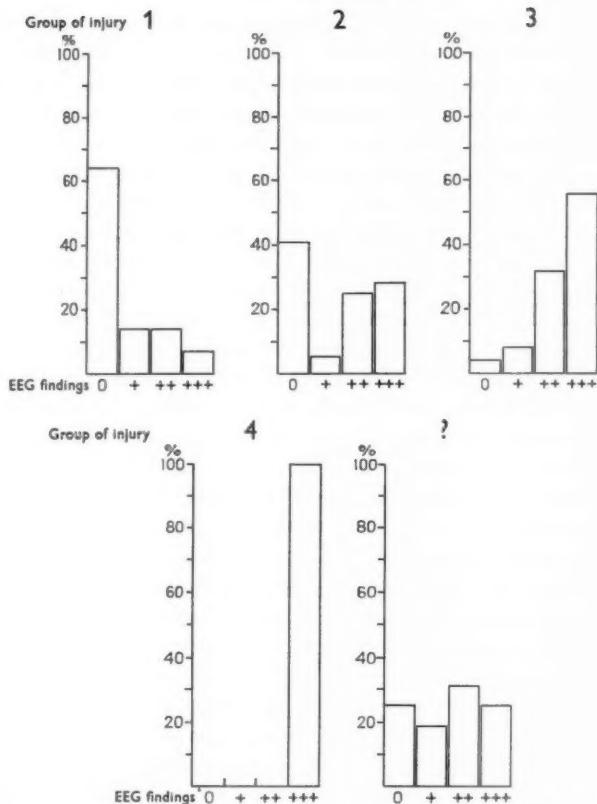


Fig. 2. Connection between nature of injury and degree of EEG findings.

occurred with greater frequency and severity. In Group 4 all the EEGs showed pronounced pathological changes upon the first examination. Yet grave EEG findings were also noted in cases which were designated clinically as mild. Against the background of earlier experiences in this field, both experimental and clinical, I am probably justified in assuming that the EEG provides a more accurate indication than the case history and clinical course. Moreover, most of these cases were

those of small children, the clinical status of whom is more difficult to ascertain.

Groups 2 and 3, on the other hand, included cases without electroencephalographic changes. Eleven of these cases were not examined until 72—96 hours after the trauma, however. Probably the results would have been different if they had been examined shortly after the injury occurred. In 1944 Dow, ULETT and RAAF found in their investigations that in cases of mild cerebral trauma abnormalities in the EEG disappeared within a period of minutes. This applied even to those patients who were unconscious for several minutes after the trauma. They considered, however, that there was no serious cerebral damage in any of these cases.<sup>1</sup> Presumably there were no more serious injuries among the cases discussed here either. Review of the clinical course supports this assumption in every case.

Within the »uncertain» group in which the circumstances connected with the injury could not be fully ascertained and the clinical course gave rise to doubts, there were all types of EEG findings. In accordance with past experience, the treatment of these cases was based on the EEG findings. When the EEG records showed marked pathological changes the patients were treated as severely injured.

In adults skull fractures are usually combined with pronounced and persistent EEG changes (among others, JASPER, KERSHMAN, and ELVIDGE 1945). This does not seem to hold true of children, at any rate not in the lower age groups. Six 0—2 year olds had skull fractures, but slightly pathological EEG findings appeared only in 2. In the age group 2—5, also, 10 cases with skull fractures showed normal or only slightly changed EEGs. In older children, on the other hand, skull fractures were regularly associated with severe EEG changes. In all there were 12 such cases.

In order to study the connection between the clinical healing process and the disappearance of EEG changes, series examinations were undertaken at as frequent intervals as circumstances permitted. As LAUFER and PERKINS pointed out in 1947, a reliable conception of the condition of the brain following trauma may be reached only by repeated examinations. The rapidity

with which the pathological EEG findings diminish and disappear is of the greatest importance in checking the progress of healing and determining the prognosis. More than 1 examination was made of in all 73 patients out of our series, all with pathological EEG changes when first examined, and within this group a total of 239 electroencephalograms were recorded, usually 3—5 examinations per patient. Of these 73 patients, 21 showed no clinical symptoms after being admitted to the hospital, even though they all showed more or less pronounced EEG changes. Fifteen patients had symptoms in the form of headaches, giddiness, nausea, vomiting, or lethargy during 1 or more of the 3 first days following the injury, after which they were free of symptoms. The other 37 patients had symptoms of the aforementioned type longer than the first 3 days and became free of symptoms only gradually. In all cases the EEG findings were both more pronounced than the clinical condition indicated and more persistent than the clinically observable symptoms.

A total of 15 patients were examined more than a month after the trauma. Of these 8 showed a normal record, while 7 still showed EEG changes. Three of the latter had nevertheless been symptom-free for a long time. In cases of this type it is probable that even before the cerebral injury the patients showed electrical activity of the kind which manifests itself as a dysrhythmic EEG. Different authors have examined control series of various sizes including normal persons in different age groups. These investigations have indicated that more or less abnormal records are found in 15%—30%; the variations in percentage are probably due mainly to variations in the rigidity of the requirements set by the authors in question for the appearance of a normal record (HILL and WATTERSON 1942; SECUNDA and FINLEY 1942; HENRY 1944; FREY 1946; KENNARD and WILLNER 1947). If in a case of cerebral injury one makes an isolated electroencephalographic examination and finds a generally abnormal record, this gives no definite information concerning the patient's actual condition following the injury. It is only when series examinations show changes in the appearance of the record that one is justified in drawing conclusions from these findings which

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may be correlated with the patient's actual injury and the healing thereof.

The 4 remaining patients who showed a pathological EEG 1 or more months after acute head injury also had clinically observable symptoms. They were all irritable and easily fatigued and showed behavior problems, although their parents stated that this had not been the case at all before the trauma. Two of them were school children whose school work became, according to their teachers, much poorer after they were injured.

It may be assumed that in patients of this type the brain is more receptive to new harmful influences. Three cases among those taken up for consideration here would seem to indicate this. In a case of a 6 year old boy, there was a second, apparently less serious trauma about 2 weeks after the original one. An EEG examination made a few days later showed a record with considerably more pronounced changes than the patient had shown when examined previously. In spite of the less serious nature of the second trauma, its effect on the brain appeared to be considerably greater, and the result was a markedly pathological EEG. The second case involved a 7 year old boy who still showed a pathological though improved EEG some 5 months after the original trauma (Fig. 3). When after his summer vacation he reported to the laboratory for a check-up examination with the object of obtaining permission to begin school, his EEG showed very marked deterioration. An interview with his mother revealed that a few days before he had run into a truck while riding a bicycle and struck his head on the street. He had not fainted or shown other symptoms, however. As he was very anxious to return to school, he had persuaded his mother not to mention the second accident. Thus in this case also when a previously injured brain encountered a new trauma considerably milder than the first, the result was a strikingly pathological EEG record.

It is not merely new traumata which appear to occur in these connections, however. After a severe skull injury (Type 4) a 3 year old girl showed a markedly pathological EEG. About  $1\frac{1}{2}$  months after the injury she was much improved both clin-

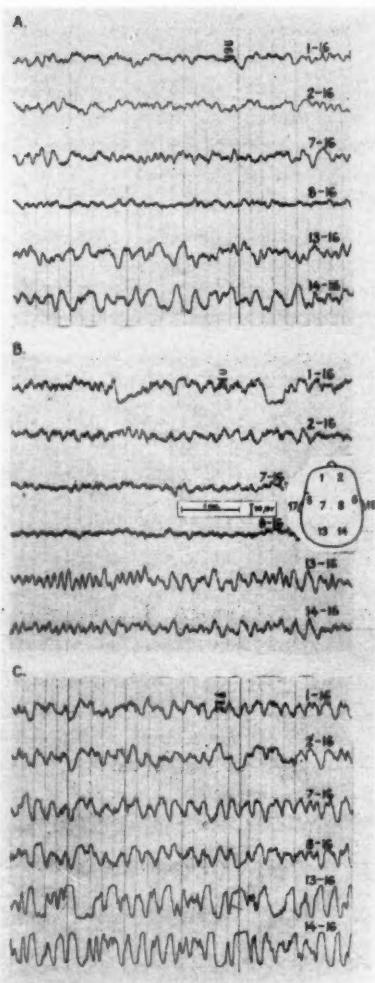


Fig. 3. 7 year old boy. A. 7 days after trauma. B. 5 months after trauma. Record still pathological. C. 3 months later, a few days after a new trauma.

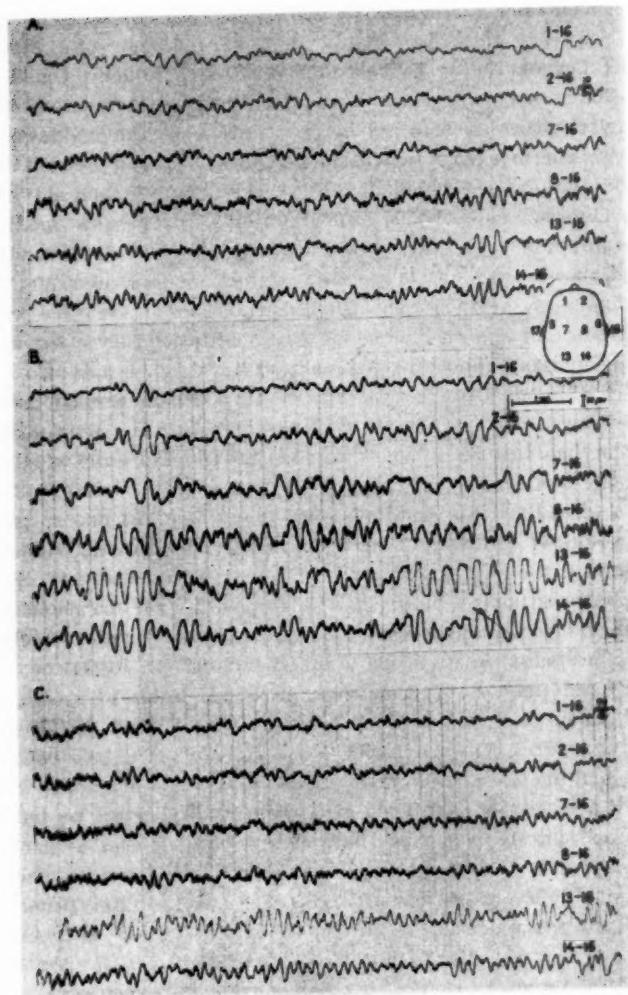


Fig. 4. 3 year old girl. A. Healing state,  $1\frac{1}{2}$  months after trauma. B. 14 days later, a few days after severe angina. C. 10 days later.

ically and electroencephalographically, but she contracted a severe angina with a fever of c. 40° C. which lasted about 6 days. After she had been without fever for a few days a new EEG was taken. It proved to be extremely pathological, in appearance closely resembling that found in encephalitis. Thus a severe throat infection apparently gave rise here to an encephalitic process, something which the brain in its injured condition following the skull trauma was probably predisposed to develop. Since the patient was being cared for in the out-patient department, a lumbar puncture, which might have verified the diagnosis of encephalitis, could not be made. The course of the disease and the relatively rapid improvement in the EEG would seem to indicate that the diagnosis was correct, however.

The EEG changes observed in the patients examined have consisted partly of varying degrees of general dysrhythmia, often combined with more or less pronounced hypersynchronia, and partly of repeated bursts of groups of 2—5/sec. waves of large amplitude (150—> 200 microvolts). In isolated severe cases depressed activity could be established at the first examination, with very slow waves of small amplitude. The most serious changes always appeared at the first examination; thereafter gradual improvement could be observed. The rapid activity noted in certain patients by JASPER and his co-workers was not in evidence in our series.

In 18 cases there were localized EEG changes: amplitude asymmetry between the hemispheres 8 times (Fig. 5) and focal changes 10 times (Figs. 6 and 7). In 11 of these 18 cases there were skull fractures, 8 in conjunction with focal findings and 3 in conjunction with hemisphere asymmetry. For the sake of comparison it may be mentioned that in the rest of the material there was skull fracture with general EEG changes in 11 cases and with normal EEG in 7, 5 of which were in children under 2 and 1 in combination with fracture of the base of the cranium. In the cases in which focal findings accompanied fracture of the skull the EEG changes appeared with 1 exception within the region in which the fracture was localized. In 1 case the focal finding was in the immediately adjoining region. In hemisphere

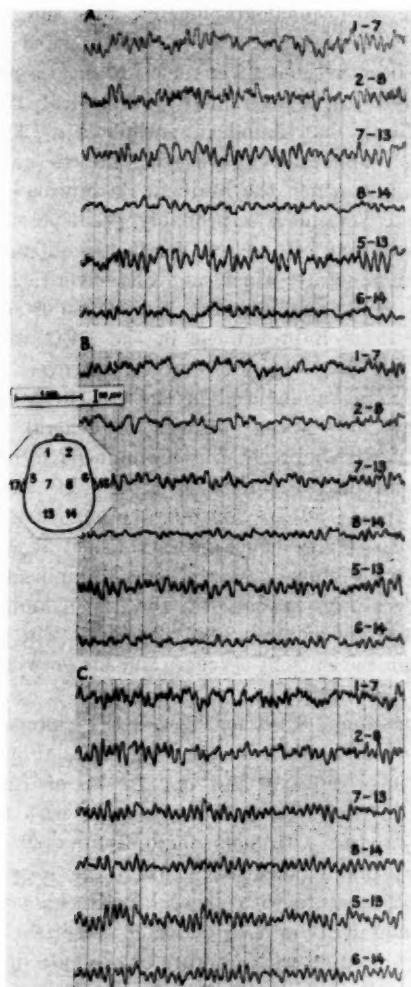


Fig. 5. 11 year old boy with fracture in right occipital region. A. 1 day after trauma. B. 10 days after trauma. C. 1 month after trauma. Marked hemisphere asymmetry, gradually decreasing.

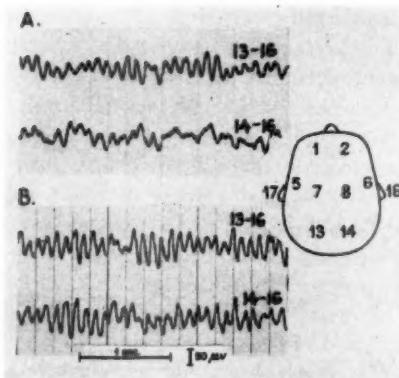


Fig. 6. 7 year old boy with fracture in the right occipital region. A. 10 days after trauma. B. 1 month after trauma. Focal finding, which disappears completely.

asymmetry also the more pronounced pathological findings were made on the side of the fracture.

In 15 of the 18 cases with localized findings EEG check-up examinations could be kept up over a sufficiently long period. In all of these the localized findings disappeared again. Hemisphere asymmetry seems to disappear most rapidly; in this series it was gone after 3-6 days. The focal findings, on the other hand, persisted in the majority of cases for 2-4 weeks. Presumably it is of great importance that patients with focal findings are followed up with care. Experiences with adults indicate that it is above all among these that cases of traumatic epilepsy are recruited.

The examinations carried out hitherto in cases of acute head injury in children admitted to Kronprinsessan Lovisa's Children's Hospital have established beyond doubt the usefulness of electroencephalography as a complement to the clinical examinations which have been available up to now. As has already been shown in the case of adults, the EEG findings correlate well with the clinical course in children also. Both when estimating the severity of an injury and when following the healing process, regular EEG

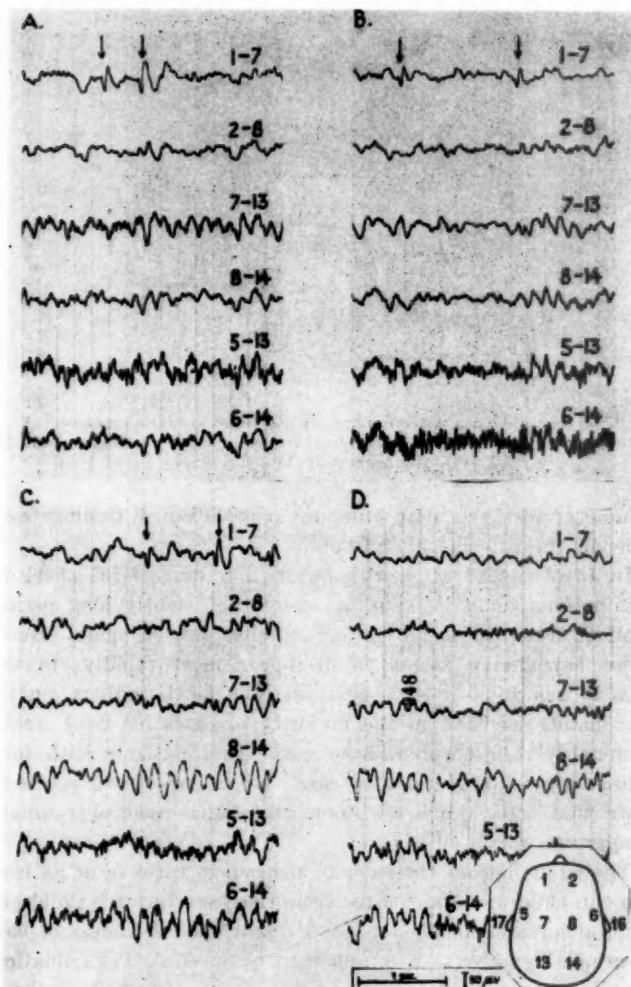


Fig. 7. 3 year old girl with concussion. A. 13 days after trauma. B. 17 days after trauma. C. 23 days after trauma. D. 35 days after trauma. Focal finding which disappears completely.

examinations mean that the condition with which the physician is confronted may be recorded more objectively and with greater certainty than before. Pathological EEG changes are not so specific, however, that they may simply be linked one by one with various pathological changes in the brain. Although in, for example, fractures of the skull focal findings occur to a certain extent within the region in which the fracture is located, general findings of different types are nevertheless more common. These EEG records can be utilized correctly only when they are combined with accurate data concerning the clinical course. Hence it is very important that the EEG examinations should in no wise be permitted to exclude a careful clinical study of the patients. The best results are obtained when the clinician and the EEG laboratory cooperate closely.

#### Summary

In order to investigate the special problems involved in electroencephalographic examinations following upon acute head injuries in children, EEG examinations of 134 children with such injuries were made at Kronprinsessan Lovisa's Children's Hospital. Seventy-two of the children were examined within 24 hours and 117 within 4 days after the trauma.

There were EEG changes among all injury groups, but with increasing frequency, so that most of the pathological findings were among the most severely injured.

Investigation of the connection between the type of injury and the severity of the EEG changes showed that within the slight injury groups a large number of EEGs were normal or only slightly changed, while the most severely injured all showed markedly pathological records. As in adults, skull fractures in older children were usually combined with pronounced and persistent EEG changes. In smaller children this did not seem to be the case.

Studies of the connection between the clinical healing course and the disappearance of EEG changes showed good correlation between the two. In all cases, however, the EEG findings were both more pronounced than the clinical condition indicated

and more persistent than the clinically observable symptoms. Over a month after the trauma 7 patients showed a pathological record. Four of these had persistent symptoms.

In children whose injuries are healing a new trauma seems to produce a proportionally more powerful effect than the first.

The EEG changes observed included general dysrhythmia of various degrees, often combined with more or less pronounced hypersynchronia, bursts of large 2—5/sec.-waves, and in isolated cases so-called »depressed activity». In 18 cases there were localized findings, in 11 in connection with fractures of the skull.

Electroencephalography is a valuable method of examination in cases of acute cerebral injury in children. It is an effective complement to the clinical examinations and in a large number of cases permits objective recording both of the nature and severity of the injury and of the healing process.

#### Résumé

Dans le but d'étudier les problèmes spéciaux se rattachant aux examens électroencéphalographiques après une lésion aigüe à la tête chez les enfants, on a fait, à l'hôpital d'enfants »Kronprinsessan Lovisa» l'électroencéphalographie de 134 enfants: 72 dans les 24 heures et 117 dans les 4 jours suivant le trauma.

Des changements EEG se sont produits dans tous les groupes de lésions mais en fréquence croissante de sorte que les changements pathologiques sont les plus nombreux dans les cas les plus graves.

L'étude de la relation entre la nature de la lésion et le degré des changements EEG a montré que dans le groupe des cas bénins la majorité des EEG sont normaux ou peu changés, tandis que les plus gravement lésés ont tous montré de fortes courbes pathologiques. Comme chez les adultes, les fractures du crâne chez de grands enfants sont souvent suivies de changements EEG prononcés et restant longtemps. Cela ne semble pas être le cas chez les petits enfants.

L'étude de la relation entre le cours de la guérison clinique et la disparition des changements EEG a montré une bonne corrélation. Cependant, dans la totalité des cas les changements EEG ont été plus prononcés que l'état clinique ne l'indiquait et

ont subsisté plus longtemps que les symptômes cliniques perceptibles; 7 patients ont, plus d'un mois après le trauma, présenté une courbe pathologique, parmi eux 4 présentaient encore des symptômes.

Chez des enfants lésés, un nouveau trauma durant la phase de guérison semble causer un effet proportionnellement plus fort que le premier.

Les changements EEG observés ont été des dysrythmies généraux de différents degrés, souvent en conjonction avec une hypersynchronie plus ou moins prononcée, nombre de grandes ondes: 2—5 sec.-et, dans des cas isolés, des «depressed activity». Dans 18 cas, des changements localisés se sont produits, dans 11, en relation avec fracture du crâne.

L'électroencéphalographie est une méthode d'examen de grande valeur dans les cas de lésion aigüe chez les enfants. Elle complète essentiellement les examens cliniques et permet dans un grand nombre de cas une transcription objective, si bien de la nature de la lésion et son degré de gravité, que du cours de la guérison.

#### Zusammenfassung

Im Laufe des Studiums der speziellen Probleme, die mit elektroenzephalographischen Untersuchungen nach akuten Kopfverletzungen bei Kindern verknüpft sind, wurden 134 Kinder mit solchen Beschädigungen im »Kronprinsessan Lovisas Barnsjukhus« EEG untersucht, davon 72 innerhalb 24 Stunden, 117 innerhalb 4 Tagen nach dem Trauma.

EEG Veränderungen traten in allen Verletzungsgruppen auf, jedoch in steigender Häufigkeit in der Weise, dass sich die meisten pathologischen Befunde bei den am schwersten Beschädigten zeigten.

Die Untersuchungen über den Zusammenhang zwischen Art der Verletzung und Grad des EEG Befundes zeigte, dass in der Gruppe der leichten Schäden eine Anzahl EEG normal oder nur leicht verändert waren, während die am schwersten Beschädigten stark pathologische Kurven aufwiesen. So wie bei den Erwachsenen sind Schädelbrüche bei grösseren Kindern gewöhn-

lich mit ausgesprochenen, lange andauernden EEG Veränderungen verbunden. Bei kleineren Kindern scheint dies nicht der Fall zu sein.

Studien über den Zusammenhang zwischen dem klinischen Heilungsverlauf und dem Verschwinden der EEG Veränderungen haben ein gutes Übereinstimmen gezeigt. Die EEG-Befunde waren jedoch in sämtlichen Fällen sowohl mehr ausgesprochen als der klinische Zustand andeutete, als auch länger andauernd als die klinisch bemerkbaren Symptome. 7 Patienten zeigten länger als einen Monat nach dem Trauma eine pathologische Kurve. Von diesen boten 4 bleibende Symptome dar.

Bei verletzten Kindern im Heilungsstadium scheint ein neues Trauma einen verhältnismässig stärkeren Effekt zu bewirken, als das erste.

Die beobachteten EEG Veränderungen waren generelle Dysrhythmien verschiedener Grade, oft kombiniert mit mehr oder minder ausgesprochener Hypersynchronie, Anhäufung von grossen 2—5/Sek. Wellen und einzelne Fälle sog. »depressed activity«. In 18 Fällen kamen lokalisierte Befunde vor, bei 11 Fällen in Zusammenhang mit Schädelbrüchen.

Die Elektroencephalographie ist eine wertvolle Untersuchungsmethode bei Fällen von akuten Kopfverletzungen bei Kindern. Sie ergänzt ganz wesentlich die klinischen Untersuchungen und erlaubt in einer grossen Zahl der Fälle eine objektive Registrierung sowohl der Art und Schwere der Schädigung als auch des Heilungsverlaufes.

### Sumario

A fin de estudiar los problemas especiales que tienen relación con las investigaciones electro-encefalográficas después de lesión aguda del cráneo en los niños, han sido examinados electro-encefalográficamente 134 niños del Hospital Kronprisessan Lovisa, todos los cuales presentaban lesión de esta clase, 72 a las 24 horas y 117 a los 4 días después de la trauma.

Se han presentado modificaciones electro-encefalográficas en todos los grupos, pero con frecuencia creciente, o sea que la

mayoría de los hallazgos patológicos han tenido lugar en los más gravemente lesionados.

Al estudiarse la relación entre la clase de la lesión y el grado del hallazgo electro-encefalográfico, se ha visto que, en los grupos de lesiones ligeras, muchos electro-encefalogramas son normales o presentan pocas modificaciones, mientras que en los gravemente lesionados las curvas patológicas han sido muy fuertes. Lo mismo que en los adultos, las fracturas del cráneo en los niños mayores están combinadas generalmente con modificaciones electro-encefalográficas pronunciadas y persistentes durante bastante tiempo. Parece que esto no ocurre en los niños más pequeños.

Los estudios de la relación entre la marcha clínica de la curación y la desaparición de las modificaciones electro-encefalográficas han mostrado una buena correlación. Los hallazgos electro-encefalográficos han sido en todos los casos, sin embargo, más pronunciados de lo que el sistema clínico había indicado y más persistentes que el síntoma clínico observable. 7 de los pacientes han mostrado, pasado un mes después de la trauma, una curva patológica. De éstos, 4 han seguido teniendo síntomas.

En niños lesionados en estadio de curación una nueva trauma parece que produce efectos proporcionalmente más fuertes que la primera.

Las modificaciones electro-encefalográficas observadas han sido disritmias generales de distintos grados, combinadas muchas veces con hipersincronía más o menos pronunciada, grandes ondas de 2—5 segundos y casos aislados de la llamada »depressed activity». En 18 casos se han encontrado hallazgos localizados, once en combinación con fracturas del cráneo.

La electro-encefalografía es un valioso método de investigación en los casos de lesiones del cráneo en los niños. Completa en forma esencial los estudios clínicos y permite en gran número de casos registrar objetivamente tanto la clase de lesión y su grado de gravedad como la marcha de la curación.

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FROM THE PEDIATRIC CLINIC OF KAROLINSKA INSTITUTET AT KRON-  
PRINSESSAN LOVISA'S CHILDREN'S HOSPITAL AND THE STATE BACTE-  
RIOLOGICAL LABORATORY.

## Pemphigus Neonatorum in Maternity Hospitals

An epidemiological study

by

GUNNEL MELIN and GÖSTA WALLMARK

*Pemphigus neonatorum* holds a predominant place among the diseases that attack new-born children in hospital maternity wards. It is true that the disease generally is benign but because of its highly contagious character it is a major problem in the affected wards. In spite of the most rigorous hygienic measures, the infection sometimes continues to pervade a ward for months. At other times its appearance is more epidemic, one case after another appearing within a short time. Isolated cases occur occasionally.

The disease has long been a subject of keen interest from the bacteriological point of view and there have been numerous investigations into its etiology and mode of contagion, in Sweden by WINBLAD and his collaborators in 1946 and others. It may now be considered as established that *Pemphigus neonatorum* is caused by staphylococcus aureus. It has been possible in recent years to divide the staphylococci into types partly serologically (COWAN 1939) and partly with the aid of bacteriophages (FISK 1942, WILSON and ATKINSON 1945). Extensive and valuable investigations based on serological type determination have been conducted by many authors including KRAGH-ANDERSEN (1943), KNOTT and BLAIKLEY (1944) and ALLISON and HOBBS (1947).

The typing of staphylococci has made easier the recognition of the sources of infection. As for mothers, the investigations of recent years in this field have afforded little evidence that

they function to any appreciable extent as primary sources of infection. In cases in which pathogenic staphylococci have been proved to exist in the breast milk, it has actually been possible to demonstrate that in all probability they have originated with the children (DUNCAN and WALKER 1942). On the other hand, it has been found that the ward staff frequently transfer the disease. ALLISON and HOBBS have shown that in an epidemic of pemphigus staphylococci of the same type occurred both in the children's pemphigus vesicles and in the respiratory tract of a number of the nurses, not only when the epidemic was at its height but from its very outset, a fact which the authors considered substantiated the theory that the infection was carried from the nurses to the children. A simultaneous occurrence of the bacteria in great numbers in the air and in dust and in the children's bedclothes etc. was believed to derive from the nurses' bacterial reservoirs, i. e. in the majority of cases from their nasal mucous membrane. Studies in recent years of infections acquired in hospitals have shown that persons with purulent skin affections frequently harbour bacteria not only in the pus but also in the upper respiratory tract. It is just these persons who often are highly contagious (MILES, WILLIAMS and CLAYTON-COOPER 1944, LAURELL 1948, MELIN 1949). In consequence those who are secondarily infected may be attacked by pyoderma or an infection of the respiratory tract, or by both infections at the same time.

Provided these investigations carry convincing weight, the vesicle-bearing children should be suspected to be important spreaders of infection, although, of course, it is also possible that the ward staff, parents and others are capable of harbouring and transferring infection. — In the literature published so far the general idea has been expressed that the infection is introduced into the ward by adult carriers, affected children serving as a source of infection principally for the staff, who then in their turn infect other children. It is true that some authors have assumed the possibility of direct infection from child to child via nursing tables, bath tubs etc., but it has not been possible to produce any conclusive evidence thereof.

### Materials

The investigations have been mainly carried out in a ward including twentythree bassinets at the maternity ward of S:t Erik's Hospital in Stockholm, where some cases of pemphigus occurred among the new-born children in June 1947. Samples were taken on the 15th and 16th June. At the time of the investigation two sick children were being cared for in the ward, while two had just been discharged as no longer in need of hospital care. Owing to the lack of isolation rooms, the two sick children were put to bed in a large telephone booth. None of the other children in the ward, nor any member of the staff nor the mothers, showed any clinical signs of infection.

In direct connection with this investigation, similar samples were made in a maternity ward at another hospital, where no case of pemphigus neonatorum had been recorded for the past six months. Besides, this ward had been closed during a week for cleaning.

### Methods

*Taking specimens.* On two consecutive days specimens were taken with an ordinary throat swab from all twentythree children in the ward from throat, nose, hands and clothes and from the pemphigus vesicles of the two sick children. Similar specimens were likewise taken from the staff in the ward (thirteen persons) and from the mothers of the two sick children. The swabs taken from hands and clothes had been previously moistened in sterile broth. The specimens from the hands were taken from both the dorsal and the volar sides, those from the clothes at a spot corresponding to the coatlapel. In this way 304 specimens were taken. — Samples were also taken (with swabs moistened with broth), from the floor dust in the two nurseries, the children's common nursing room and the isolation booth. In addition, for the bacteriological investigation of the air, sedimentation plates (see LÖFSTRÖM, LAURELL, OUCHTERLONY 1948) containing blood agar or phenol-mannitol-agar were exposed in these four rooms for six hours.

*Culture.* The swabs were streaked on a blood agar plate and a phenol-mannitol-agar plate according to CHAPMAN (1945) after which each swab was inoculated in serum broth. The blood-agar plate was read after incubation over night at 37°, the phenol-mannitol plate after a further twentyfour hours at roomtemperature. Suggestively yellow staphylococci were recultured on agar slants, inoculated in broth and subjected to a coagulase test (0.5 ml plasma + 0.1 ml culture broth, incubated at 37° for three hours, read immediately and after twenty hours, at roomtemperature). The broth culture was inoculated intraperitoneally in mice after six hours incubation at 37° for isolation of pneumococci.

*Type determination.* All coagulase-positive strains of staphylococci were typed by means of bacteriophages. Fourteen different phages were used, nine of which were isolated by Wilson and Atkinson and five at the Swedish State Bacteriological Laboratory by Wallmark. The technique will be described in a coming paper. It may be stated here, however, that with these fourteen phages has been constructed a scheme containing eighteen different staphylococcus types (table I). As seen in the table the strains have been given numbers from one to thirteen. The staphylococci isolated from the pemphigus follicles etc., however, (see below) did not belong to any of the types mentioned above. They were only partly (but clearly) lysed by a single phage (819). For convenience we will call these bacteria »819». In all, seventy-three strains were examined. A type determination was made of only one colony from each sample. The strains from the control material were not typed.

### Results

*The epidemic at the maternity ward.* The presence of pathogenic staphylococci will be seen from Tables II and III.

Eighteen out of the twentythree children, the two sick children's mothers and six of the staff were carriers of pathogenic staphylococci in their upper respiratory tracts. In addition, staphylococci were found on the hands and in the clothes of fifteen children, one mother and three members of the staff. The occurrence of the different types is also shown.

*Table I.*  
Key for typing staphylococci.

Phage type	Bacteriophage filtrate													
	3 B I	6 II	7 III	42 B IV	47 C V	3 C VI	47 VII	7 B VIII	51 IX	K S 6 X	819 XI	1034 XII	166 XIII	155 IV
1 A	+++	—	—	—	—	+++	—	—	—	—	—	—	—	—
1 B	+++	—	—	—	—	+++	—	(+)	—	—	—	—	—	—
2 A	—	+++(+)	—	—	—	+++	—	—	—	—	—	—	—	—
2 B	—	+++(+)	++	++	++	++	—	—	—	—	—	—	—	—
2 C	—	+++(+)	(+)	(+)	(+)	(+)	—	—	—	—	—	—	—	—
3	(+)	+++(+)	—	(+)	—	—	—	—	—	(+)	(+)	(+)	(+)	(+)
4	—	—	—	+++(+)	—	—	—	—	—	—	—	—	—	—
5 A	—	—	—	—	—	—	—	—	(+)	—	—	—	—	—
5 B	—	—	—	(+)	—	—	—	—	(+)	—	—	—	—	—
6	—	—	—	—	—	—	—	—	—	—	—	—	—	—
7	—	—	—	—	—	—	—	—	—	—	—	—	—	—
8	—	—	—	—	—	—	—	—	—	—	—	—	—	—
9	—	—	—	—	—	—	—	—	—	—	—	—	—	—
10	—	—	—	—	—	—	—	—	—	—	—	—	—	—
11 A	—	++	(+)	+	—	++	—	—	(+)	—	—	—	—	(+)
11 B	—	—	—	—	—	—	—	—	—	+	—	—	—	—
12	—	—	—	(+)	—	—	—	—	—	—	—	—	—	—
13	—	—	—	—	—	—	—	—	—	—	—	—	—	—

+++ : confluent lysis with no or slight secondary growth

++ : confluent lysis with secondary growth or semiconfluent lysis

++ : numerous isolated plaques

(+) : 10—50 isolated plaques

— : less than 10 plaques or no lysis.

Table II.

No. examined	Children		Follicles	Mothers		Staff		Air and dust
	Throat	+ nose		Throat	+ nose	Throat	+ nose	
	Hands	+ clothes		Hands	+ clothes	Hands	+ clothes	
	23		2	2		13		
Staphyloc. carriers	18	15		2	1	6	3	
Type 2 A	7	7		1		2	1	Nursery II
Type »819»	4	4	2			1		Nursery I
								Service room
Type 4	1							Isolation booth
Type 13	1	1		1	1			
No type	8	4				3	2	Isolation booth

The individual distribution of the types of staphylococci among the children is reported in table III, which also contains an account of the age of the children and the rooms in which they had their beds.

It will be seen from the table that staphylococci could be obtained from the pemphigus follicles of the two sick children (9 and 23). Staphylococci of the same type (»819») were also found in the upper respiratory tract of these children. This type was also isolated from the throat of one child (5) and of one of the staff, and from the nose and throat of one child (7), though none had any clinical symptoms whatsoever. In one child (18) the above type was found on the hands, and in two (3 and 16) in the clothes. Further, staphylococci of the same type were found in abundant quantities in the floor dust and in the air in nursery I, also in the service room and in the isolation booth (table II). Some of the children were simultaneously carriers of more than one type (e. g. one type in the throat, another in the nose). In one case (patient 17) there was found an abundance of staphylococci not only in the nose and throat but also on hands and clothes within the first 24 hours.

Table III.

The distribution of the different staphylococcal types among the children.

Child No.	Age in days	Nose	Throat	Hands	Clothes	Follicles	Nursery
1	1						Nursery I
2	4	2 A	N. T.	2 A	2 A		9 9
3	7				819		9 9
4	16	N. T. <sup>1</sup>					9 9
5	4	2 A	819				9 9
6	4	2 A	4	N. T.			9 9
7	14	819	819				9 9
8	17	N. T.			2 A		9 9
9	7	819	819			819	9 9 (Isol.)
10	1			2 A			Nursery II
11	4	2 A	2 A	2 A			9 9
12	21	2 A	2 A	2 A			9 9
13	33		N. T.				9 9
14	<1 <sup>2</sup>						9 9
15	9	N. T.	N. T.	N. T.	N. T.		9 9
16	5		N. T.	N. T.	819		9 9
17	1	12	12	12	12		9 9
18	3	N. T.	N. T.	819			9 9
19	7	N. T.	N. T.				9 9
20	4	2 A	2 A	2 A	2 A		9 9
21	19	2 A	2 A		2 A		9 9
22	2			N. T.	N. T.		9 9
23	7	819	819		819	819	9 9 (Isol.)

The age indicated denotes the 1st day of taking specimens.

<sup>1</sup> N. T.: not typable.

<sup>2</sup> Admitted to the ward on 16.6.

In not a single case were there found any  $\beta$ -haemolytic streptococci. One member of the staff was found to harbour pneumococci type 4 in the nose, and another to harbour pneumococci type 3 in the throat.

*The control material.* The results from the control material will be found in Table IV.

*Table IV.*

The control material.

	Children		Staff		Air and dust
	Throat + nose	Hands + clothes	Throat + nose	Hands + clothes	
Total	15		10		
Staphyloc. carriers	13	12	2	1	Nursery I Nursery II

Out of the fifteen children in this ward, thirteen were found to have pathogenic staphylococci in the upper respiratory tract, and out of the ten members of the staff two were carriers of staphylococci. In one of the staff and twelve children the bacteria also occurred on hands and in clothes, and both in the air and in the dust from the nurseries an abundance of staphylococci were found.

In this ward also there was not a single case of  $\beta$ -haemolytic streptococci. Pneumococci type 3 were found in the throat of one of the staff.

#### Discussion

The results are in close accord with those obtained elsewhere, chiefly in England. There is every indication that in wards in which pemphigus neonatorum is present there are pathogenic staphylococci dispersed in extraordinary numbers among both children and adults, as well as in the air and dust.

It would appear, however, that these bacteria occur to a great extent among the children even in wards free from pemphigus. In view of this fact it is conceivable that only certain strains of staphylococci may produce this infection.

It is probable that staphylococci belonging to type »819» were the cause of the pemphigus epidemic investigated. It is, however, impossible to judge in which way this type was introduced into the ward. It may have been one of the staff, one of the mothers, some visitor or a child that had already been infected in the maternity ward. Probably the bacteria spread further both directly and indirectly, for example, via the air, floor dust, nursing table, and the bath.

Prior to their isolation the two sick children were nursed in different rooms, i. e., the one in nursery I and the other in nursery II. In nursery I type »819» were found in the throat and nose of one child, in the throat only of another, and in the clothes only of a third. The simultaneous mass discovery of bacteria in the air and floor dust indicates the presence of a so-called »dangerous carrier» (HAMBURGER 1946). It is most probable that this carrier is to be found amongst the children, as the only member of the staff who could be proved to be a carrier of this type was in the room infrequently, and then only for short periods. The child that was most suspected was the fourteen-days-old baby (No. 7), which had an abundance of bacteria in both throat and nose. This child may conceivably have acted as source of infection in at least one of the cases of pemphigus (No. 9).

In nursery II the bacteria were found in two children, though in the one case only in the clothes (No. 16) and in the other only on the hands (No. 18). No bacteria were found either in the air or in the dust from the floor. A discovery of these bacteria only on the hands or in the clothes may mean either that they occurred so sparsely in the upper respiratory tract that, in spite of the double tests, attempts to isolate them failed, or else that they had been conveyed from outside. In this case it is most probable that the children acquired the bacteria on hands and clothes in conjunction with nursing, either directly from the nurse, who was a nasal carrier, or from the air, dust or a nursing table in the room.

The presence of other types also throws light on the spreading of staphylococci. — Type 12 occurred in only one child, the one-day-old (No. 17). This child, however, was a carrier in

both throat and nose, and besides, he had bacteria on his hands and in his clothes. This means that he was a dangerous carrier in the Hamburger sense. There is every indication that this child had been infected in the maternity ward, and as he had been only a few hours in the nursing ward he had no time to spread the bacteria there. — Type 2 A occurred in 8 children, of whom 5 were born on the same day. This, too, indicates that any possible infection must have come from the maternity ward.

In summary, it may be said that the results of the investigation support the idea that the spreading of staphylococci proceeds in several ways. It would appear that mass infection may take place already in the maternity ward, though it is probable, that the bacteria more commonly occur in the nursing ward. The staff, and possibly the mothers as well, act as carriers of the infection. Moreover, we feel that the children also contribute actively to the spreading of the infection, not only, through their acting as sources of infection for the staff (ALLISON and others), but also by secreting abundant quantities of bacteria that find their way to the air, floor dust, baths, nursing tables etc.

### Summary

During a minor epidemic of pemphigus neonatorum occurring in a maternity ward, bacteriological investigations were carried out. The isolated staphylococci were typed with the aid of bacteriophages.

The staphylococcus causing pemphigus was not possible to put into the type scheme but reacted in a characteristic way to one phage. This same type also occurred in some healthy children and in the air and the floor dust.

Besides the members of the staff, the newly born babies also appear to have played a considerable part in spreading infectious agents.

The investigation carried out in a ward that was free from pemphigus yielded just as abundant an occurrence of staphylococci. The epidemiology of pemphigus neonatorum is discussed.

**Résumé**

Durant une légère épidémie de pemphigus du nouveau-né dans une section de maternité, on a fait des examens bactériologiques. Le type des staphylocoques trouvés, a été déterminé à l'aide de bactériophages.

Le type de staphylocoques ayant causé le pemphigus du nouveau-né n'a pu être classé dans le schéma des types, mais il réagissait d'une manière caractéristique à l'action d'un phage. On a trouvé le même type chez quelques enfants en bonne santé ainsi que dans l'air et dans la poussière du plancher.

Outre les membres du personnel, les nouveau-nés semblent donc avoir joué un grand rôle comme transmetteurs de germes.

Un examen parallèle fait dans une section sans pemphigus a montré une aussi grande abondance de staphylocoques.

L'épidémiologie du pemphigus du nouveau-né est discutée.

**Zusammenfassung**

Auf einer Gebäraabteilung, wo eine kleine Epidemie von Pemphigus neonatorum ausgebrochen war, wurden bakteriologische Untersuchungen gemacht. Die Typen der gefundenen Staphylokokken wurden mit Hilfe von Bakteriophagen bestimmt. Der Staphylokokkentypus, welcher den Pemphygus verursachte, konnte nicht in das Typschema eingeordnet werden, aber er reagierte auf eine karakteristische Weise mit einer Phage. Den-selben Typ fand man auch bei einigen gesunden Kindern, sowie in Luft und Bodenstaub. Ausser dem Personal haben nach Allem zu schliessen, die neugeborenen Kinder eine grosse Rolle als Ansteckungsverbreiter gespielt.

Eine Paralleluntersuchung auf einer Abteilung, die frei von Pemphygus war, zeigte ein ebenso reichliches Vorkommen von Staphylokokken.

Die Epidemiologie des Pemphygus neonatorum wird besprochen.

**Resumen**

Durante una pequeña epidemia de pénfigo neonatal que apareció en una sala de maternidad, se efectuaron investigaciones

bacteriológicas. Los estafilococos aislados se clasificaron con ayuda de la bacteriofagía.

No fué posible colocar los estafilococos causantes del pénfigo en un cuadro de tipos, pero reaccionaron de una manera característica de un fago. Este mismo tipo se encontró también en niños sanos y en el aire y polvo del piso.

Fuera de los miembros del personal, parece que los recién nacidos participaron también bastante en la propagación de agentes infecciosos.

Una investigación efectuada en una sala libre de pénfigo demostró una abundante presencia de estafilococos. Se discute la epidemiología del pénfigo neonatal.

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FROM THE PEDIATRIC CLINIC OF KAROLINSKA INSTITUTET AT KRON-  
PRINSESSAN LOVISA'S CHILDREN'S HOSPITAL, STOCKHOLM. (CHIEF: PRO-  
FESSOR A. LICHTENSTEIN.)

## Pulmonary Insufficiency

by

**HANS-OLOF MOSSBERG**

During recent years the diagnosis of the congenital heart diseases and cardiac insufficiency have especially been subject to much interest. The pulmonary insufficiency, on the other hand, has only been studied by few workers, although dyspnoe and cyanosis both are included in the symptomatology of cardiac and pulmonary insufficiency. That difficulties at times may arise with regard to the interpretation of a condition of insufficiency is illuminated by the case history of a patient who in September 1948 was admitted to Kronprinsessan Lovisa's Children's Hospital (Record N:o 1046/48).

The case was that of an 11-year-old girl who was referred to this hospital for cardiac study and possibly operation of a suspected congenital heart disease. The major symptoms were a suggested dyspnoe and cyanosis when sitting in bed, marked reduction of function on exertion and pronounced clubbing of fingers and toes.

The earlier case history reports a normal development in the first years of life, with absence of feeding problems, bowel disturbances or other signs of disease. From the age of 4 years onwards the patient's appetite became poorer, she became easily fatigued at play, and had an increased susceptibility for nosocomial infections. After the age of 6 she has had 2 severe pneumonias, one of which was associated with bilateral otitis, 2 severe attacks of angina, measles, severe pertussis, repeated bouts of bronchitis with fever, and between whiles a nearly permanent cough. After the age of 6 the parents observed that the fingers gradually changed and became clubbed. They also observed an increasing shortness of breath and cyanosis on exertion, which invalidized the girl to a con-

siderable extent. She now is unable to walk more than 50 meters on level ground without resting. She is not a squatter.

When the patient in 1944 at the age of 7 was to begin school she was examined at the local hospital, where a soft systolic murmur over the entire heart was heard. A "congenital heart defect" was considered present. She began school but had difficulty in keeping up. At a X-ray examination in the spring of 1948, at 11 years of age, widespread changes of the lungs were established. The patient was examined at a sanatorium, whereby she was found to be Mantoux negative to 3 mg, the pulmonary findings being suspected to be due to chronic stasis of the lungs, brought about by a congenital vitium. The patient was referred to this hospital for further study.

Examination on admission showed a thin pale girl, weighing 28 kg (normal weight in relation to the height 33.8 kg, according to Broman, Dahlberg and Lichtenstein's height—weight tables); she was 141 cm tall (normal height for the chronologic age 139.2 cm). At bed rest there was no dyspnea or cyanosis. After even a slight movement in bed there appeared a slight *dyspnea* and *cyanosis* of the lips. Fingers and toes showed pronounced *clubbing*. The heart was normal in size. The first sound was blurred but without a distinct murmur. The second sound was divided and accentuated. Blood pressure 120/80. Over both lung fields was heard a vesicular breath sound and scattered small harsh râles. The abdomen was soft and nontender. The liver was palpated 2 to 3 fingers breadth below the costal margin at about the level of the umbilicus, and had a smooth soft surface. Galactose tolerance test and bromsulfalein test were normal. The Schlesinger test in the urine was markedly positive. The tymol test was 8 units and Meulengracht 1:8, which is somewhat augmented. Takata showed a deep and broad spike as in cirrhosis of the liver and in chronic pulmonary processes. The spleen was not palpable. Neurologically there was nothing pathological. Wasserman was negative. Complete blood status showed normal values (Hgl 78 % = 12.0 g%, red cells 4.18 millions, white cells 8400, thrombocytes 260 000). The bone-marrow showed slight reactive changes but no specific features (NORDENSON). The Heller and Almén tests were also negative. Nonprotein nitrogen 23 mg%. Renal function tested with creatinine clearance was normal (91 ml/min). Diastase in the urine 16 units.

Already at the first examination at this hospital suspicion was directed towards the lungs. *Intracardiac catheterization* (MANNHEIMER) and *angiocardiology* (ULFSPARRE) showed entirely normal conditions of pressure and flow in the cavities of the heart. Cardiac X-ray showed a small drop heart ( $235 \text{ ml/m}^2$  body surface); circulation time 16 sec; venous pressure 7 cm. On the *electrocardiogram* were observed changes of the incomplete AV block type, which with Wilson leads was shown to consist of a right bundle-branch block.

On the *chest X-ray* was observed a finely spotted parenchymal density giving the pulmonary fields a mosaic-like structure. On the suspicion of bronchiectasis *lipoidal bronchographies* were done on both lungs, although with negative results (ULFSPARRE).

*Tentative diagnosis: Pulmonary fibrosis.*

No definite signs of a general fibrosis of the entire body with reduction of functions were demonstrable in the organs examined.

In order to determine the type of the pulmonary insufficiency a number of tests of pulmonic function were carried out, according to COURNAND & RICHARDS.

COURNANDS & RICHARDS (1941) distinguish between 4 types of pulmonary insufficiency:

- I. Ventilatory insufficiency (= insufficiency of the breathing mechanism).
- II. Respiratory insufficiency (= insufficiency of the alveolar gas interchange).
- III. Combined ventilo-respiratory insufficiency.
- IV. Combined cardio-pulmonary insufficiency.

The ventilatory insufficiency is thus largely mechanical. Its major symptom is the dyspnoe. The respiratory insufficiency is physicochemical and its major symptom is cyanosis due to anoxia. If the ventilatory insufficiency is severe enough the respiratory function of the alveoli also will be impaired. Besides, in respiratory insufficiency the respiratory centre will owing to blood chemical reasons receive added stimulus, this augmenting the ventilation. This motivates the occurrence of the third group. That conditions of pulmonary insufficiency may give rise to symptoms of cardiac insufficiency as well as a primary cardiac insufficiency conversely may give rise to a pulmonary insufficiency is well known. These cases are included in the fourth group.

The *ventilatory insufficiency* is due to a decrease of the maximal breathing capacity or to an increase of the breathing requirement, or to a combination of both. By *maximal breathing capacity* is implied the maximal voluntary power of ventilation per minute, the patient choosing depth and rate of breathing. The *breathing requirement* is the actual ventilation requirement per minute at any given point of time. This is determined partly with the

patient supine and under basal conditions, partly following exercise (e. g. Bing's standard exercise test). The difference between the maximal breathing capacity and the breathing requirement is the *breathing reserve*. According to COURNAND & RICHARDS the dyspnea threshold is reached when the breathing reserve has decreased to 60 or 70 per cent of the maximal breathing capacity.

The *vital capacity* has also been determined.

The *respiratory insufficiency* is determined, as already mentioned, by a disturbance of the alveolar gas interchange. The *effectivity of the alveolar function* is measured by calculating the consumption of oxygen and the elimination of carbon dioxide at rest and at exercise, e. g. Bing's standard exercise test, and also by *analysis of the arterial blood*. At a satisfactory alveolar function the arterial blood will have a high degree of oxygen saturation, approximately 95 per cent.

These investigations, described by COURNAND & RICHARDS, have been carried out on our patient. As, however, standard values are lacking for the age group of the patient, I have on 4 hospital patients without cardiac or pulmonary disease carried out all of these tests, with the exception of the determination of the arterial oxygen saturation. Owing to inter alia MANNHEIMER's experience, however, we know that the arterial oxygen saturation in children normally does not fall below 90 per cent, wherefore the statistically calculated normal values of COURNAND & RICHARDS are entirely applicable as comparable values. The values obtained in the present case are depicted in Table I, and show in comparison with the normal values as follows:

A severe reduction of the maximal breathing capacity and the vital capacity is present, concomitantly with an increased breathing requirement at rest, which is in agreement with the findings of KALTREIDER & McCANN (1937) in pulmonary fibrosis in adults. These conditions induce a breathing reserve close to the dyspnea threshold, which is in good agreement with the clinical findings.

Also the intake of oxygen and the output of carbon dioxide at rest and at exercise show marked pathological values, which

Table I

All values computed per m<sup>2</sup> body surface.

also are in correspondence with a pathologically low arterial oxygen saturation.

The diagnosis of pulmonary insufficiency was made; — probably pulmonary fibrosis secondary to chronic inflammations of the lungs. The insufficiency was a combined ventilatory and respiratory insufficiency, secondarily giving rise to hepatic changes, to bundle-branch blocking, and to a pronounced clubbing of fingers and toes. The presence of a general fibrosis has not been substantiated either by the history or the findings.

The case is illustrative as an example of the symptomatic similarity between cardiac and pulmonic insufficiency with dyspnea and cyanosis, and also throws light on the possibilities for analysis and specific diagnosis that we now possess.

*After discharge* from the hospital the patient felt well during the 2 following months; she was afebrile and was ambulatory. In the beginning of January 1949 she fell ill with acute pneumonia and a left-sided acute pyelonephritis and three days after

the onset she died in the local hospital. Autopsy showed that our diagnosis was correct.

*Autopsy findings (MUNKE):* The lungs were heavy and firm and lacked the normal aerated texture. On the surface of the lungs there were hundreds of emphysema vesicles the size of the head of a pin. On section of the lungs there was felt a tenacious resistance. There were no bronchiectases. There was a pronounced fibrosis of both lungs, probably localized to the pulmonary lobes and the alveolar septa. In the right lung there was also in the greater portion of the middle and lower lobe a carnification of the pulmonary parenchyma in several areas. In the right middle and lower lobe there was observed a rather widespread pneumonic infiltration of the red hepatization stage.

The heart was normal in size and contracted. There was possibly a moderate dilatation of the right ventricle and the right auricle. The tricuspid and the mitral valves were of normal width and without vegetations. There were no septal defects. Foramen ovale was closed. The myocardium was macroscopically normal.

The liver weighed 1 100 gm. It was markedly enlarged. The section showed a pronounced marking.

The spleen was a normal sized infection spleen.

The kidneys; the right kidney was normal in size. The left kidney showed yellowish-white streaks in the medulla and pus in the renal pelvis.

*Histologic examination (S. OLSSON): Lungs:* In all of the pulmonary lobes there are observed changes similar in principle although of varying degrees. The interalveolar septa are nearly everywhere more or less thickened and fibrous, with rather abundant contents of lymphocytes, plasma cells and here and there a number of polynuclear leucocytes. The fibrous alveolar septa contain rather abundant wide vessels, well filled with blood. The alveolar lumina are small, very rarely aerated, generally filled with thick nearly colloid-like fluid, desquamated epithelium, macrophages and in certain areas numerous leucocytes. The cellular elements of the pulmonary alveoli contain abundant droplets of fat. Here and there are observed fibrin masses with signs of organization. The alveolar epithelium is high, mainly cuboid and often absent or substituted with polynuclear giant cells. In or adjacent to these are often found narrow crystalliform cavities, as after liberated cholesterol crystals. The bronchi are somewhat widened in areas with abundant streaks of non-striated muscle in the walls and covered with common partially desquamated bronchial epithelium. The fibrosis is not especially pronounced around the bronchi. Peribronchially there is found a moderate leuco-lympho-plasmocytic infiltration. The interlobular

interstices are moderately increased in breadth, fibrous and often considerably edematous, containing inflammatory elements. There are no definite vascular changes.

*Myocardium:* The muscle fibres are often somewhat thickened but show for the rest no certain intravital changes.

*Liver:* Markedly widened partially bloodfilled capillaries, especially in the peripheral acini. The hepatic cellular walls are markedly atrophic and the cells show a rather pronounced fatty degeneration.

*Spleen:* Bloodfilled, partially hyperplastic splenic pulp with fairly abundant polynuclear leucocytes.

*Kidney:* Abundant blood in greater and lesser vessels, for the rest no pathological changes.

*Diagnosis:* *Lungs:* Chronic pneumonia with particularly abundant diffuse interstitial fibrosis. *Liver:* Chronic stasis. *Spleen:* Chronic and acute stasis with suggested pictures of so-called infection spleen. *Kidney:* No essential changes.

The most conspicuous symptom in the present case was the clubbing of fingers and toes. The pathogenesis of clubbing is not clearly understood. Some workers consider the changes to be the consequence of a disturbance in the nutrition of the tissues owing to a vascular spasm with constriction of the venous capillaries; others consider the cause to be edema, induced by a decrease of the oxygen saturation of the blood; still others consider that the cause is an augmentation of the peripheral circulation. The anoxia theory enjoys the greatest popularity but definite proofs are lacking in all of these theories. In the present case we know that a decreased arterial oxygen saturation is present and that this probably has been the case for several years.

I have in the literature not been able to find a report of pulmonary fibrosis in children of the age of this patient, although there are many studies on such conditions in adults. This indicates that the disease is considerably less common in childhood than in adulthood. There are not either any detailed studies on the pulmonary function in children. Thus, there remains much to investigate in the field of pediatric pulmonary diagnosis and pulmonary pathological physiology.

**Summary**

A case of pulmonary insufficiency in a girl of 11 with pulmonary fibrosis and pronounced clubbing of the digits is described. The pulmonary function was investigated according to the schedule of COURNAND & RICHARDS. Autopsy findings confirmed the diagnosis of interstitial pulmonary fibrosis. The case illustrates the symptomatic similarity between cardiac and pulmonary insufficiency with dyspnoe and cyanosis and also the present day means of analysis and specific diagnosis.

**Résumé**

Un cas d'insuffisance pulmonaire chez une fillette de 11 ans ayant une fibrose pulmonaire et des doigts hippocratiques prononcés. La fonction pulmonaire a été examinée d'après le schéma de COURNAND & RICHARDS. L'autopsie confirme le diagnostic de fibrose pulmonaire interstitiel. Le cas met en lumière la similitude symptomatique entre l'insuffisance cardiaque et l'insuffisance pulmonaire avec dyspnée et cyanose ainsi que les possibilités d'analyse et de diagnostic spécial que l'on a aujourd'hui.

**Zusammenfassung**

Es wird ein Fall von Pulmonaler Insuffizienz bei einem 11-jährigen Mädchen mit Lungenfibrose und ausgeprägten Trommelschlägelfingern berichtet. Die Lungenfunktion wurde nach dem COURNAND & RICHARDS Schema untersucht. Die Sektion bestätigte die Diagnose: interstitielle Lungenfibrose. Der Fall illustriert die Symptomgleichheit zwischen cardialer und pulmonaler Insuffizienz mit Dyspnoe und Cyanose, sowie die Möglichkeiten zur Analyse und Spezialdiagnose, die es jetzt gibt.

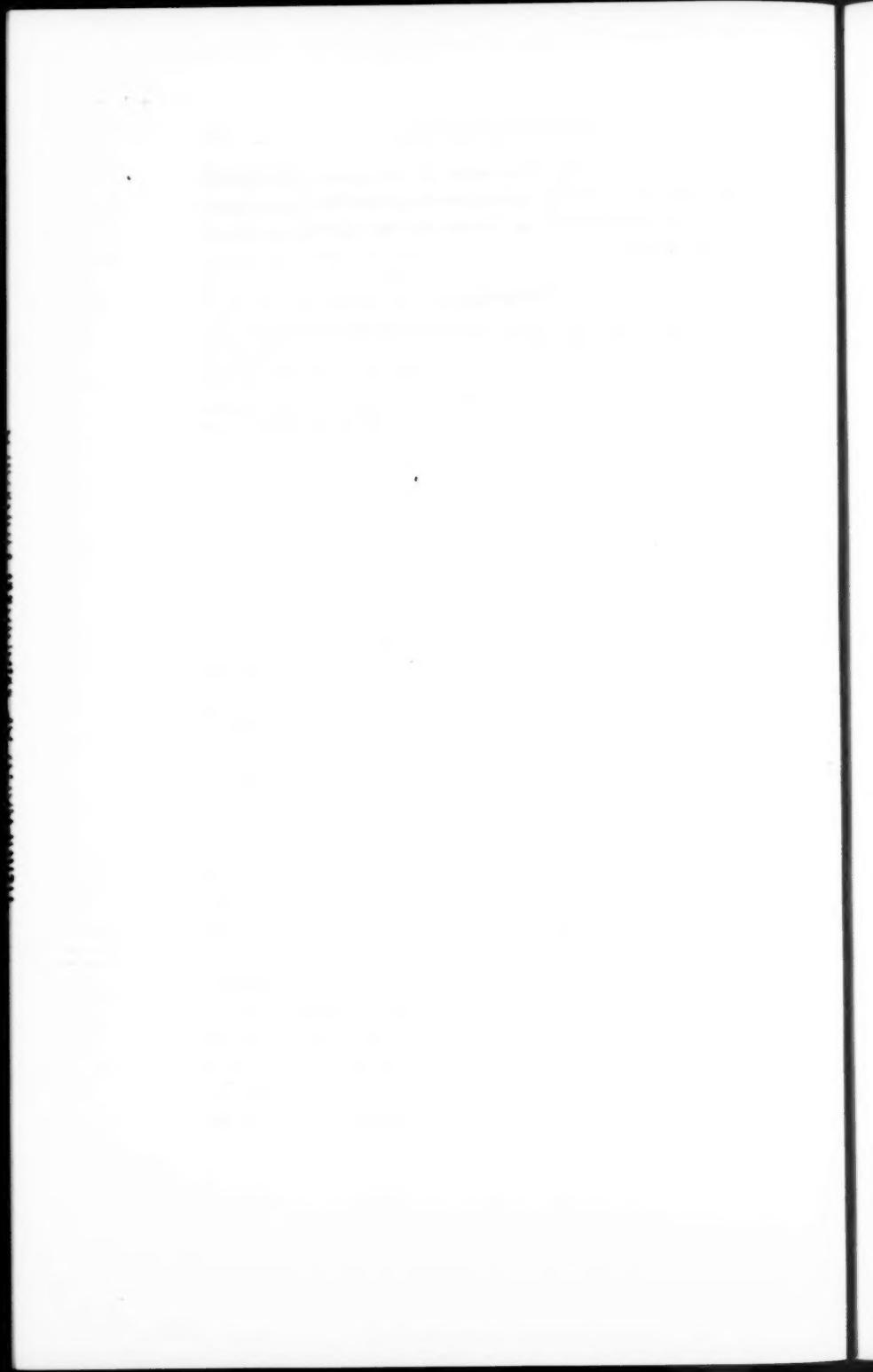
**Resumen**

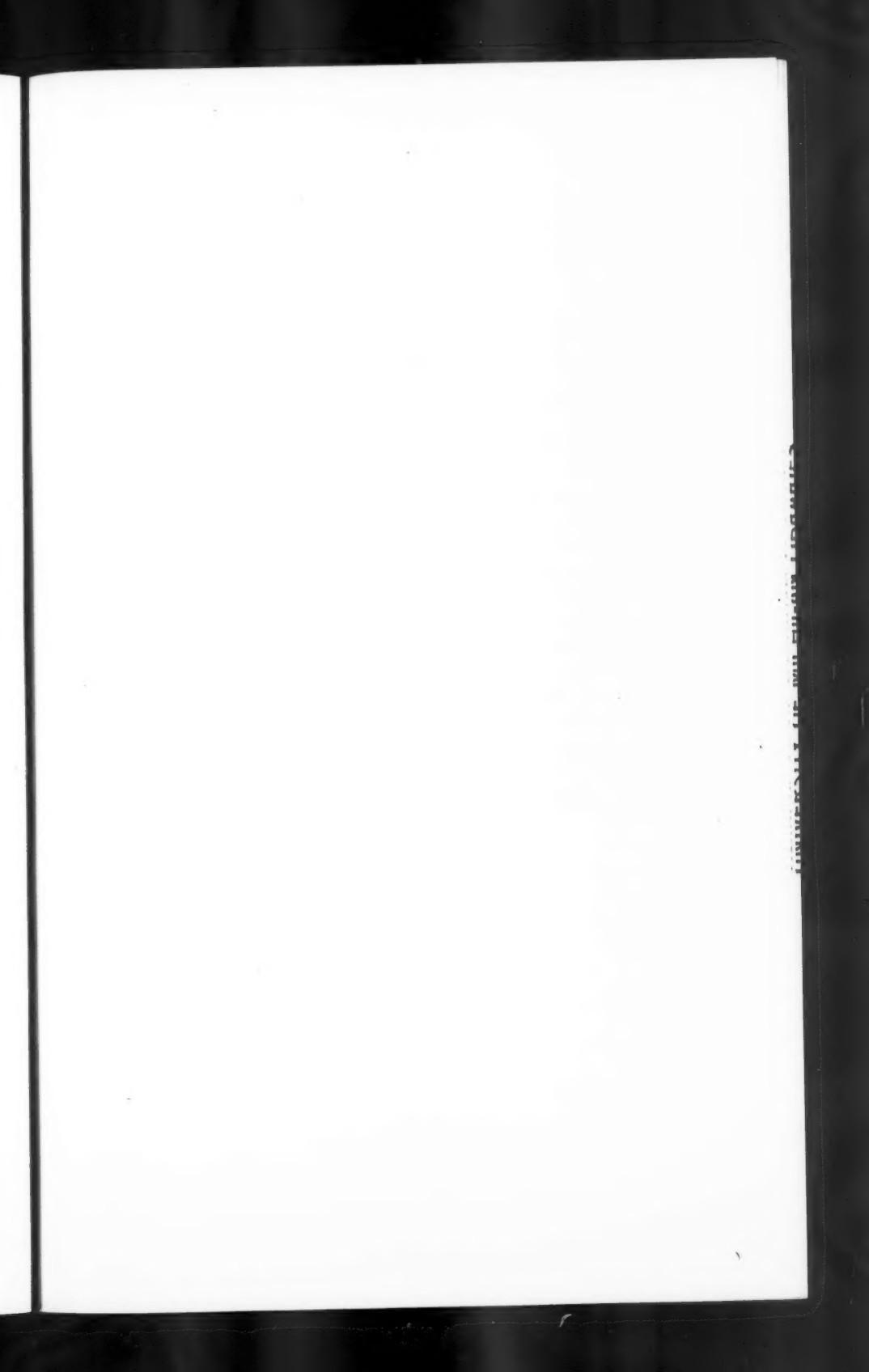
Se describe un caso de insuficiencia pulmonar en una muchacha de 11 años que tenía fibrosis pulmonar y pronunciado trabaamiento de los dedos. Se examinó el funcionamiento pulmonar de acuerdo con el plan de COURNAND & RICHARDS. Hallazgos por medio de autopsia confirmaron la diagnosis de fibrosis pul-

monar intersticial. El caso demuestra la semejanza sintomática entre insuficiencia cardíaca, insuficiencia pulmonar con disnea y cianosis, y también entre los medios de hoy día de análisis y diagnosis específica.

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APR 6 1950

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IN

FROM THE PEDIATRIC CLINIC, UNIVERSITY OF LUND, SWEDEN  
(HEAD: PROFESSOR STURE SIWE, M. D.)

# CHOREA

ITS NOMENCLATURE, ETIOLOGY AND EPIDEMIOLOGY  
IN A CLINICAL MATERIAL FROM MÄLMOHUS COUNTY

1910—1944

BY

**JOHANNES LEWIS-JONSSON**

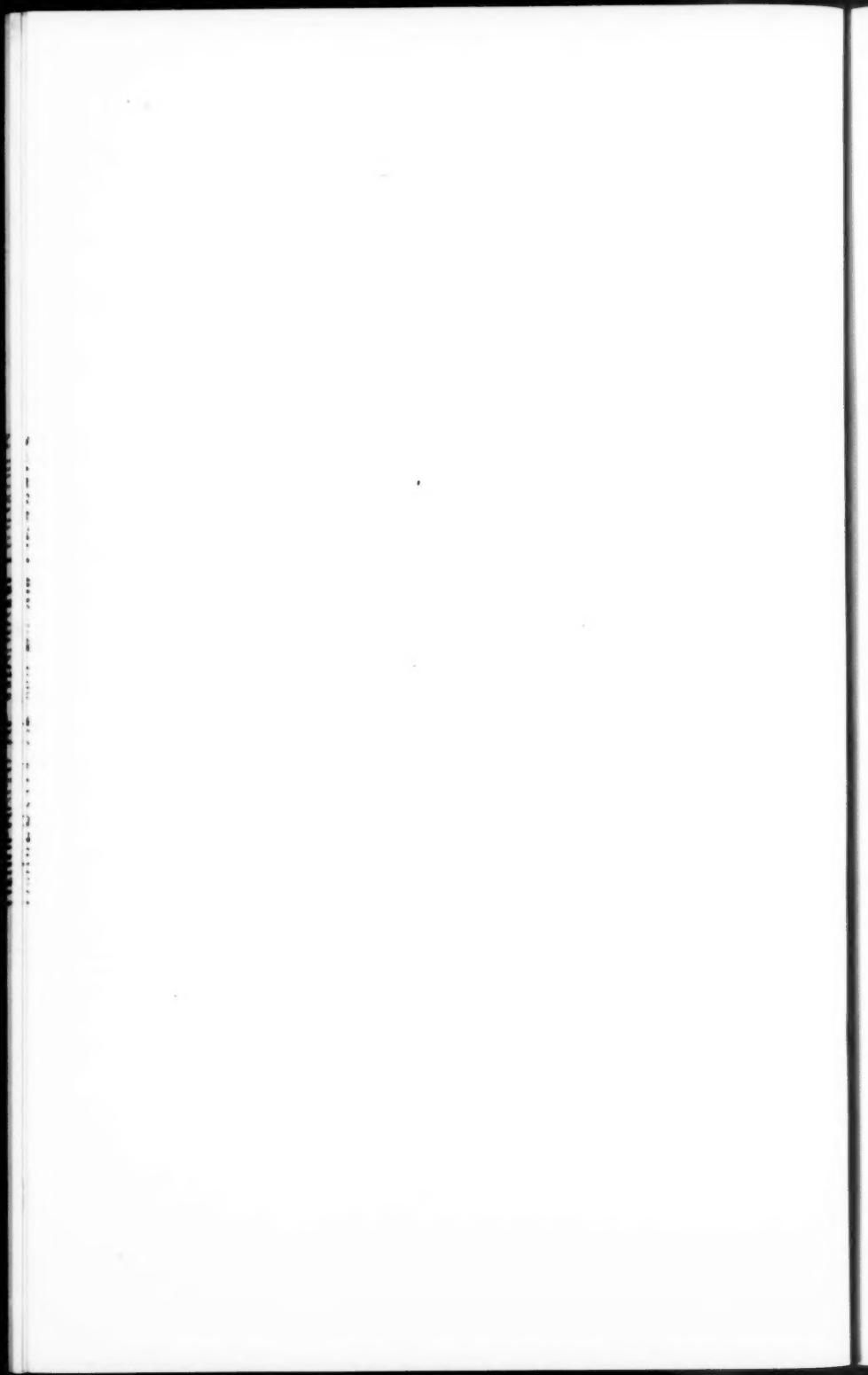
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*Stockholm 1949*

LUND  
HÅKAN OHLSSONS BOKTRYCKERI  
1 9 4 9

To My Wife  
and My Mother



## PREFACE.

To every physician the observation of chorea implies a number of problems which often are difficult to differentiate. The work here presented originated from that sensation of something problematic which chorea creates.

My first intention to tackle these problems was aroused in 1936, while as a senior medical student I was cramming for the final examination, when the comparative form »minor» in chorea minor conveyed to me an impression of some obscure »major» not clearly mentioned in the text-books. The next impulse to take up this work came in 1943 during my service as resident physician, when I had to decide whether a patient with chorea and endocarditis but no joint complaints was to be registered as a »case of rheumatic disease» in the investigation into the occurrence of rheumatic diseases in Sweden that was being carried out that year. My third and decisive intention to look into this matter was suggested in 1945, during my service as amanuensis in the Pediatric Clinic in Lund, when Professor Sture Siwe in his lectures and clinical discussions outlined all the problems involved in the term »chorea».

Just as the idea of the present work grew into a practical attempt in three stages, the work was also carried out in three stages. It was commenced in 1945, in the Pediatric Clinic of the University in Lund, continued in the Rheumatic Clinic of the Lund Hospital and concluded in the Medical Clinic of the Helsingborg Hospital. This curriculum symbolizes also that chorea is a pediatric and rheumatic as well as internal medical matter.

In the course of this work it has been of invaluable advantage to me to have had for chief and teacher such men as Professor Sture Siwe, head physician to the Pediatric Clinic in Lund, Docent Gunnar Edström, head physician to the Rheumatic Clinic in Lund, and Professor Thor Stenström, head physician to the Medical Clinic in Helsingborg. All of them have afforded me excellent working

conditions and contributed to the work with their good advice and encouraging discussion of various problems. Therefore, I shall always feel deeply indebted to them.

The material for the present studies was obtained from all the hospitals in Malmöhus county in which chorea patients had been under treatment. I wish here to give my best thanks to the chiefs of these clinics for the obliging interest they have taken in my work.

I further wish to acknowledge the kind and valuable assistance I have received from various clergymen and hospital administrators in getting the addresses of many of the patients, and likewise to the librarians in the University Library in Lund, Municipal Library in Helsingborg and in the library of Leo, Ltd. in Helsingborg.

To Professor Carl-Erik Quensel, the Statistical Institute of the University in Lund, I am greatly obliged for his kindness in carrying out the mathematic calculations in this work.

Miss Elsa Lewis-Jonsson, my sister, and Mrs. Ingmar Löfkvist have been of great assistance to me in the analysis and arrangement of the patient material for which I thank them most cordially.

The translation of this work into English was made by Dr Hans Andersen, Copenhagen, whose pleasant collaboration and painstaking care in expressing my views I greatly appreciate.

Financial aid for the performance of these studies has been granted me from Konung Gustav V's 80-årsfond, to the Board of which I beg to address my sincere thanks.

Helsingborg, Lasarettet, September 1949.

*J. Lewis-Jonsson*

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## INTRODUCTION.

From the large, variegated group of physical and mental diseases which in the Middle Ages were covered by the designation »St. Vitus' Dance« and which all had various muscular movements in common, Th. Sydenham (1686) isolated a characteristic clinical entity of movements limited to the years before puberty, usually unilateral and with a tendency to relapse. For this form of motional disturbance, however, he retained the earlier term Chorea St. Viti, and he failed to give any cause for the clinical picture he described. Thus, from the very start, Chorea St. Viti became a topic of discussion, as the nomenclature early became subject to innovation, and the question was raised whether Sydenham's description applied to a disease *per se* or to a group of symptoms.

On reviewing what has been written about chorea in different periods, we find, indeed, that the nomenclature has varied. Each period has tried to express its conception of chorea by changing the nomenclature. The meaning of »chorea« has not always been the same, so that sometimes there has been a shift in its meaning without any change in the nomenclature. Thus, for instance, Sydenham's chorea or chorea minor does not in our days imply the same as when these terms were first employed. In his work »On Chorea and Choreiform Affections«, William Osler (1894) says, indeed: »In the whole range of medical terminology there is no such olla podrida as chorea ...«. In a way, his remark still hits the spot — primarily because our knowledge about the cause of chorea is not much greater now than fifty years ago.

The first purpose of this work, therefore, has been to take up the current chorea nomenclature for discussion. By analyzing it in a clinical material comprising chorea of varying etiology and at the same time correlating its various forms historically, the writer hopes it will be possible to arrive at a nomenclature clinically serviceable in chorea.

The second purpose of this work is a result of the first one, namely: through studies in the literature and the present material to try to give a survey of the different causes of chorea.

Rheumatic infection is taken to be the most common cause of chorea. The connection of the two conditions has been known since Stoll in 1780 published two cases of arthritis and chorea. The relation of chorea to rheumatic infection has attracted much interest and for nearly a hundred years chorea has been reckoned as one of the most important manifestations of the acute rheumatic infection. In more recent medical research the rheumatic infection has occupied a prominent position. The goal, to establish the cause of the rheumatic infection, is yet far away, and we still have to subscribe to the words of Swift in 1929: »Rheumatism has long remained one of the riddles of medicine.» In the search for the cause of the rheumatic infection, therefore, every little detail in our knowledge may be of value.

We now know that most cases of acute rheumatic infection occur among school children, the peak of the frequency curve for patients with acute rheumatic infection appearing before the age of 10 years, and in about one half of all the cases of this disease the onset took place before the age of 20 years. Among the rheumatic manifestations chorea occupies a special position, appearing at the age when rheumatic infection most frequently sets in. Furthermore, chorea is the manifestation that is most easily observable; it is the earliest to be diagnosed, and it leaves the most reliable anamnestic data. In their monograph on the rheumatic diseases, indeed, Poynton & Schlesinger (1937) say: »We lay much stress on the fact that chorea is the most obvious clinical index of rheumatism in childhood during school life.» This implies that rheumatic chorea ought to be a good object for investigation of the epidemiology of the acute rheumatic infection.

The third purpose of this work, therefore, has been to elucidate the epidemiology of the rheumatic infection through the study of some epidemiological factors in a clinical material of rheumatic chorea. By limiting the investigation to a definite section of the population, comprising as many cases of chorea as possible, it ought to be practicable to give a contribution to the epidemiology of the rheumatic infection.

## CHAPTER I

### Definition and diagnosis.

In the literature and in the clinic the term *chorea* is used to designate partly a symptom, a certain type of motion, partly a syndrome including the choreal motion, a decrease in muscular tonus and disturbance of coordination. The term has also been applied to the disease in which the choreal motion is the dominant feature, as a rule the clinical picture of rheumatic infection. Finally, the term has been employed for a collective concept covering all the diseases having the symptom or syndrome of chorea in common.

In this work the term chorea is used merely to designate the disturbance of motility and, sometimes, also the choreal syndrome with its disturbance of motility, decrease in muscular tonus and disturbance of coordination.

As a symptom, chorea is generally characterized by a lot of involuntary, arrhythmic motions serving no purpose whatever, susceptible to excitement and accompanied by associated movements. One sequence of movements differs from the other, and as a rule the motions disappear during sleep. In the choreal syndrome there is also a lack of coordination (dysmetria, adiakokinesis, asynergia) and (or) a decrease in muscular tonus which may be so marked as to result in paralysis. The latter condition is designated as *chorea molle* or *paralytic chorea*.

The anatomical basis for chorea is not fully known, and the same applies to its physiological basis. We know that if any changes whatever are found in the brain in patients with chorea, they are most often localized to the basal ganglia, in particular to the corpus striatum (Meynert, 1868; Jackson, 1867; Anton, 1895, and others). Alzheimer (1911), C. & O. Vogt (1920) and Lewy (1923) have found changes, above all, in the small cells of the corpus striatum. Bonhoeffer (1897) observed a case of chorea with metastasizing cancer in the pedunculi cerebri; and several findings indicate

that changes in the thalamus, probably in its ventrolateral part, and in the subthalamic body of Luys most likely may also be the cause of chorea (Martin, 1928; Vipond, 1930; Kihm, 1933; Fulton, 1943). Also changes in other extrapyramidal nuclei, cerebral cortex and cerebellum have attracted attention in this respect.

Here we are dealing with a field that is exceedingly difficult to investigate. Castrén (1925), who has thoroughly studied the pathologic-anatomical changes in chorea, sums up his findings quite cautiously in the statement that nothing much may be said about the matter other than that the choreatic movements must arise as a result of cerebral disturbances involving the extrapyramidal tract. And Fulton (1943), from whose work Fig. 1 is taken, makes the following statement, in which his caution shows our stand just now: »The syndrome accompanied by involuntary movements (athetosis, chorea and torsion spasm) have no settled pathology, but they appear most frequently to be associated with lesions of the striate bodies (caudate and putamen) and brain stem nuclei; however, they often show simultaneous involvement of the red nucleus, substantia nigra, subthalamic body of Luys.»

Kihm (1933), giving a survey of the pathophysiology of chorea and of the attempts of various investigators at localization of the choreatic disturbance of the motility to a definite brain center, arrives at the conclusion that we should not seek one or more choreal centers but reckon with a *choreal system of the brain*. This system has its own, as yet unknown, physiological laws so that no matter where the injury sets in, it elicits the same symptom: chorea.

In the diagnosis of chorea a *differential diagnosis* should always be made from other hyperkinesias.

*Tic or habit spasm* differs from chorea, above all, in the fact that in tic the motion is always the same. It returns in the same muscular groups and as a rule it is a repetition of an originally expedient motion: blinking, twitching of the corners of the mouth, smacking the lips, nodding, twisting the neck, hunching the shoulders, etc. Often it is difficult to tell whether the patient is suffering from a low-grade active chorea or has developed what may be called a choreic habit spasm (Collis, 1937). Undoubtedly tic may occur simultaneously with chorea, and the transition between the two hyperkinesias is smooth. Straus (1927) even employs the term »postchoreatic tic». The differential diagnosis between chorea and

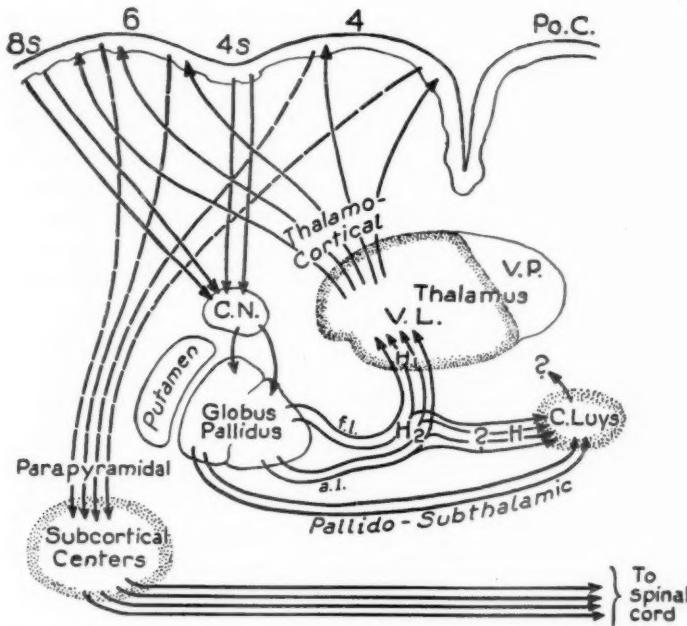


FIG. 106. Neural mechanism of choreo-athetosis. Inhibitory impulses arise from the suppressor strips 8s and 4s and pass to caudate nucleus(C.N.); they pass from there to globus pallidus; thence from internal division of *globus pallidus*(Ranson and Ranson) through *fasciculus lenticularis*(f.l.)and *ansa lenticularis*(a.l.)into field H<sub>2</sub> and through field H<sub>1</sub> into the antero-lateral part of the ventro-lateral nucleus of the thalamus(V.L.) (Papez); from there thalamo-cortical fibres return suppressor impulses to precentral cortex, more to area 6 than to area 4(Papez). If this suppressor mechanism is interrupted in *striatum*(Alexander)or *globus pallidus*(Papez)or thalamus(Schuster)the *parapyramidal* system arising from areas 4 and 6 will be released to abnormal activity resulting in involuntary movements of choreo-athetosis. This diagram also illustrates possible pathways for similar suppressor fibres from 8s and 4s to the caudate nucleus and globus pallidus and thence to the subthalamic nucleus of Luys(C. Luys)either by way of the *fasciculus* and *ansa lenticularis*, and fields H<sub>2</sub> and H<sub>1</sub>(Papez)or by way of pallido-subthalamic bundle from external division of *globus pallidus* as described by Ranson and Ranson. How these suppressor impulses return to precentral cortex is unknown but their interruption in corpus Luysi results in hemiballismus(Bucy, 1942).

Fig. 1. Diagram of neural mechanism of chorea after J. F. Fulton: Physiology of the nervous system. Oxford University Press, London 1943, Second Edition, p. 456.

tic is particularly difficult when the tic is made up of a fairly long sequence of motions. According to Lapage (1933), it is a general rule that «chorea is so much better known that tics are frequently diagnosed and treated as chorea and not vice versa».

Chorea differs from *athetosis* in that the involuntary motions in athetosis are slow and writhing in character, more pronounced in the distal than in the proximal joints, and not infrequently combined with muscular hypertonia. Torsion spasm, according to Ingvar (1934), consists in athetotic motions of the trunk when the patient is standing or walking, while they are absent when the patient is lying down. As a rule it is not difficult to differentiate chorea from athetosis, the rate of the motions being different. Sometimes quick and jerky movements complicate the slow sinuous variety, and transitions to chorea are found which are designated as choreo-athetotic or athetosis with choreatic admixture, or vice versa. Chorea and athetosis are merely groups of symptoms within the field of motility, and they may be present in any combination (Schilder, 1911).

*Hemiballismus* is a throwing movement of an arm. The arm may be hurled precipitately outward or upward, quite uncontrollably, as a rule accompanied by a rotatory movement of the trunk. According to Fulton (1943), it is due to isolated damage to the body of Luys. It is very rare and through its particular feature it should not be difficult to differentiate from chorea.

*Fidgety movements*, which are common in children, may greatly resemble a commencing chorea. The observation of disturbance of the coordination or decrease in muscular tonus may sometimes settle the question, while in other cases an observation in the customary milieu will be necessary. In rare cases the possibility of hyperthyroidism may also be excluded in this way.

A diagnosis of chorea *per se* says nothing about the nature of the lesion of the brain which gives chorea. Broadbent (1869) has formulated this view by looking upon chorea as » ... a symptom rather than a disease, which cannot be referred to any single pathological condition but as symptomatic only of the seat of the disease ... ». A conception of the cause of chorea may be obtained only through studies of the clinical milieu in which chorea is encountered.

As mentioned already in the introduction, rheumatic infection is taken to be the most frequent cause of chorea. As a matter of fact, however, the etiology of rheumatic lesions is still unsettled.

In this work the term *rheumatic infection* is employed to designate

the hypothetical cause of the rheumatic lesion. The same term is used also for the clinical rheumatic picture topical in this book. Also the designation acute rheumatic infection is used, but the prefix »acute» is not necessary in this connection, as chorea certainly has no place in the clinical picture of rheumatoid arthritis (Wissler, 1942). Rheumatic infection is the term employed, among others, by Thomson (1928), Leichtentritt (1930), Glanzmann (1935) and Friedländer (1945).

A synonym frequently used is rheumatic fever (*e. g.*, Seagel & Seagel, 1927; Swift, 1929; Edström, 1935; Paul, 1947). Other synonyms are: rheumatismus verus, given by Naegeli (1933) and employed by v. Neergaard (1934) and by Fanconi (1943), rheumatismus infectiosus specificus as given by Gräff (1934), la maladie de Bouillaud and the Bouillaud-Gräff disease, used by Aschoff (1939).

The *clinical picture* of the acute rheumatic infection is built up round the rheumatic arthritis, the picture of which was first defined by Sydenham in 1676. Stoll (1780) added chorea to the nosography of rheumatic disease, which in 1788 was extended by Pitcairn with the addition of pericarditis. In the latter part of the 18th and early part of the 19th centuries the dominating rôle of cardiac disease in the rheumatic picture was realized. In 1840 Bouillaud stated that the coincidence of the heart lesion and the joint affection is the rule, their non-coincidence the exception, and he continued: »... chez les jeunes sujets le cœur se comporte comme une articulation». It is from that time — citing v. Glahn (1947) — that we may reckon the beginning of the modern literature on »rheumatism». In 1881 Barlow & Warner gave a convincing description of the subcutaneous nodules as evidence of rheumatic infection, and through Lehndorff & Leiner (1922) the occurrence of erythema annulare was recognized as a rheumatic phenomenon. As Fanconi & Wissler (1943) puts it, erythema annulare is »die Visitenkarte des Rheumatismus verus». The coincidence between erythema nodosum and rheumatic infection was pointed out as early as 1873 by Couland, but its value as a sign of rheumatic infection was first given precisely by Wallgren (1938) in the following view: »Positive proof of a rheumatic genesis can be provided only by a case in which tuberculous infection is entirely absent».

It is chiefly the above manifestations which in our days form the clinical picture of acute rheumatic infection. The rheumatic

pleurisy, pneumonia, peritonitis, nephritis and eye changes are still difficult to appraise exactly as rheumatic manifestations and will here merely be mentioned, just like purpura and erythema exsudativum multiforme.

Gradually, as the laboratory examinations were elaborated and extended, an increasing number of signs of rheumatic infection have been recognized; especially leukocytosis, anemia and increased sedimentation rate. Further, investigations on the hemolytic streptococci have established, above all, the high antistreptolysin titer and the agglutination of hemolytic streptococci as not infrequent signs of rheumatic infection. Furthermore, pathologic-anatomical studies have established certain histological changes as specific of rheumatic infection.

Notwithstanding our increased knowledge concerning rheumatic infection, however, we have not yet obtained any specific diagnostic test. Just like in older days, we still have to base the diagnosis of rheumatic infection on clinical observations. All data in the history of the patient, his physical status and the course of his illness have to be appraised from a diagnostic and differential-diagnostic point of view, and the accuracy of this appraisal depends on human intuitiveness, clinical acuity and critique developed from bedside experience (Coburn, 1945). Accordingly, we cannot get away from the subjective factor in making the diagnosis of the rheumatic lesions. In this respect, it still holds good what Sturges (1881) said nearly 70 years ago: »... until we agree upon the particular signs and symptoms which are to be accepted as valid evidences of rheumatism, we have no common factor to deal with, and may expect the remarkable discrepancies in result which actually appear.

In our days various American investigators have tried to advance the diagnostics in acute rheumatic infection by gradating the different rheumatic manifestations in »major» and »minor» manifestations, requiring for the diagnostic value of these manifestations a difference in the frequency of their occurrence to indicate the diagnosis of rheumatic infection. This technique was first suggested by Swift (1929), although he did not employ the nomenclature mentioned. But this was adopted, among others, by Kaiser (1934), Headly (1940), Wilson & Lubschez (1944) and Jones (1944); in Sweden it has been employed by Jacobsson (1946). All the authors agree that the arthritis, carditis, chorea and subcutaneous nodules

are major manifestations, but the concordance extends no further. Kaiser, for instance, reckons also rheumatic pneumonia, rheumatic pleurisy and purpura as major manifestations, and Jones as well as Jacobsson reckon the »tendency to recurrence» as a major manifestation. The concordance of the authors is no greater with regard to »minor manifestations» (fever, high sedimentation rate, leukocytosis, anemia, abdominal pains, epistaxis, etc.). Thus the employment of these terms is precluded already by the difference in the importance attached to them.

Therefore, until the etiology of the rheumatic infection is established or a specific diagnostic test is worked out, any author dealing with the problems of rheumatic infection will still have to state his view of the infection and give his diagnostic criteria — in other words, as Jones (1944) puts it: »... some confession is inevitable».

In the present work where it often has to be decided whether or not a given instance of chorea is due to rheumatic infection, the following criteria for rheumatic infection are employed in the appraisal of the clinical material:

I. Arthritis. (The acute migratory or polycyclic polyarthritis with swelling and redness of the joints requires no discussion. But the joint pains, muscular pains and growing pains occurring in children are difficult to appraise as diagnostic criteria. Here I prefer to follow Shapiro (1936) who thinks that »growing pains» have no rheumatic etiology. The rheumatic infection gives a more constant pain, is more often located to the joint itself, more often to the upper extremities than to the lower, and it more often is relieved somewhat by the warmth of the bed, while it may give stiffness of the joint in the morning.)

## II. Chorea.

III. Carditis. (Endocarditis, myocarditis, pericarditis and their sequelae are diagnosed on the criteria given in »Nomenclature and Criteria for Diagnosis of Diseases of the Heart», edited by the Criteria Committee of The New York Heart Association, New York, 1946).

## IV. Subcutaneous nodules.

**V. Erythema annulare Leiner.****VI. Erythema nodosum with negative tuberculin reaction.****VII. Rheumatic granuloma (observed on biopsy or autopsy).**

For the recognition of a case of rheumatic infection *at least two* of the above-mentioned criteria must be present in the same patient. There is no definite chronological sequence in the appearance of the manifestations, but no other cause of the manifestation must be demonstrable. The rheumatic diagnosis has to be both positive and negative.

In this work chorea occurring in a patient together with any of the above-mentioned rheumatic manifestations in the history or state of the patient or in the course of the case is recorded as *rheumatic chorea*.

Chorea occurring in a patient presenting definite signs of some other cause of the chorea is recorded primarily as *non-rheumatic chorea*.

Chorea occurring in a patient without any of the above-mentioned criteria or definite signs of some other cause is recorded as *cryptogenic chorea*.

## CHAPTER II.

### Material.

#### 1. Character, Composition and Limitations.

The aim was to obtain a material as representative of chorea as possible, especially with regard to nomenclature, etiology and epidemiology.

The material is gathered from all clinics and asylums in Malmöhus county where cases of chorea have been under treatment. The material covers the period of 1910—1944.

Malmöhus county and its population offer some favorable conditions for the investigations planned. The borders of the county have not been altered during the period mentioned; and the county has not been visited by war or plagues. An increase in the total population as well as in the total number of inhabitants in the higher age-classes, together with an increased urbanization, are the most important changes that have occurred. These changes are well established through the censuses taken within the period covered by this investigation. The results of these censuses with regard to the number of inhabitants in all age-classes and at the age of 0—14 years are distributed on the rural and urban populations as shown in Table 1.

The total population has increased, but the younger age-classes have diminished; the increase in the total number is greater for the urban population, and the decrease in the count for the younger age-classes is more pronounced for the rural districts.

In the following calculations more figures on the population are employed than those given in Table 1; all figures, however, are taken from *»Sveriges officiella statistik«*.

In Malmöhus county the public care of the sick throughout the period here concerned has functioned so that it has been possible, if required, for every patient to get under treatment in a hospital.

Table 1. Number of inhabitants of any age in Malmöhus county and of 0—14 years, distributed on country and town at the censuses on 31/12 1910, 1920, 1930, 1935, 1940 (and 1945).

Year	No. of inhabitants of any age			No. of inhabitants of 0—14 years		
	Total	Country	Town	Total	Country	Town
1910	457,214	282,097	175,117	142,545	90,267	52,278
1920	487,459	253,656	233,803	139,674	76,444	63,230
1930	510,607	259,843	250,764	122,083	69,646	52,437
1935	518,903	241,477	277,426	110,502	59,001	51,501
1940	530,185	223,746	306,439	104,776	50,858	53,918
1945	551,610	217,437	334,173	115,023	48,993	66,030

The examination and care of the choreic patients have practically been the same throughout the period. Recent extension of the hospital with laboratories and roentgenological clinics has made but little difference in the diagnostic aspects of chorea.

The delimitation of the period to 1910—1944 was made for practical reasons. A large material and an observation period as long as possible were desirable; at the same time, however, each case should have been observed thoroughly, and this requirement may sometimes be in conflict with the long observation period — at any rate, the longer the observation period, the less frequent are the observations in the case records. This is noticeable, above all, prior to 1920; and to obtain a material representative of chorea prior to 1910 is simply impossible. The upper limit of the observation time was decided by the commencement of the working-up of the present material.

The collation of the material was carried out by going through the annual reports from the hospitals where choreal patients conceivably have been under treatment. The number of cases mentioned in the annual report are looked up in the ledger, the number of the special record is obtained, and the data given here are transferred to a Keysort card; and in this way a chorea card index was obtained which permits assortment of the material from different points of view. Every case with «chorea» in the diagnosis is included, even though chorea was merely suspected.

Table 2. *Distribution, after the annual reports, of 1026 hospitalized cases of chorea in the clinics of Malmöhus county in 1910—1944.*

Town	Hospital	Clientele	Period	No. of cases	Remarks
<i>Lund</i>	Ped. Clinic	Children	1910—1944	222	
	Med. Clinic	Adults	1910—1944	123	
	Gyn. Clinic	Women	1910—1944	20	
	Psych. Clinic	Adults	1928—1944	7	
	Rheumat. Clinic	Adults	1928—1944	2	
<i>Malmö</i>	Flensb. Children's Hosp.	Children (< 7 yrs.)	1913—1944	7	
	Malmö Children's Hosp.	Children	1910—1944	149	From 1943, convalescent home
	Med. Clinic	All pts.	1910—1944	166	
	Gyn. Clinic	Women	1910—1944	8	
	Neurol. Clinic	Adults	1931— $\frac{13}{4}$ 1940	10	Department 15.
	Psych. Clinic	All pts.	1936—1944	1	Department 5.
	Epidemic Hosp.	All pts.	1923—1944	3	Department of infectious diseases
<i>Helsingborg</i>	Banck Children's Hospital	Children	1910—1944	47	Prior to Sept. 1944: Children's Hospital
	Med. Dep.	All pts.	7/8 1925— 1944	56	
	General Hospital	All pts.	1910— $\frac{6}{5}$ 1925	46	
	City Maternity and Gyn. Hosp.	Women	17/4 1926— 1944	0	
<i>Hörby</i>	General Hospital	All pts.	1910—1944	41	
<i>Landskrona</i>	General Hospital	All pts.	1910—1944	36	
<i>Trelleborg</i>	General Hospital	All pts.	1910—1944	45	
<i>Ystad</i>	General Hospital	All pts.	1910—1944	37	
			Total	1026	

Table 2 gives the 20 clinics in Malmöhus county in which the archives from 1910 to 1944 have been gone through with reference to chorea, and the distribution of the hospitalized cases according to the annual reports, a total of 1026 cases.

In some instances the annual reports of the clinics have not been available, and then the number of cases entered in the ledger has been assumed to equal the number given in the annual report. In the case of one clinic both the annual report and the case records are lacking for 1910—14 and 1918—19, owing to accident. For this clinic, in the given periods, the number of patients admitted for chorea, 19, was obtained from the annual reports kept in the Central Archive in Stockholm.

On going through the archives of the clinics, the writer has not been able to find exactly the same number of patients admitted as given in the annual reports, a deficit for 7 clinics, a surplus for 2. In spite of considerable efforts it has not been possible to avoid a difference of 30 cases, of which the majority is made up of the 19 above-mentioned cases.

In the archives of the clinics, thus, 996 cases of chorea are found in the records. The missing 30 cases make 2.9% of the total given in the annual reports.

The actual number of persons with chorea, however, is smaller than the number of hospital cases, as some patients have been hospitalized repeatedly under the same diagnosis. Such persons are here registered under the hospital and year of their first admission. A survey of the number of first visit cases and return cases is given in Table 3, which shows the 996 hospital cases being distributed on 791 persons.

Inquiry into the domiciles shows that of the 791 individuals 33 are from another county and thus not representative of the population of the Malmöhus county. So the final result is that in the clinics of Malmöhus county during the period of 1910—1944, altogether 758 inhabitants of this county were hospitalized with chorea.

From an entirely hospital-administrative point of view it may be of interest to see from what kind of clinics these 758 cases of chorea are collected. Fig. 2, p. 25, shows that about the same number of cases of chorea were treated in pediatric and medical departments, nearly 80% altogether, while about 20% of the total were treated in general hospitals, and only a few per cent in special clinics.

The material obtained by going through the case records does not always contain sufficient information for its working-up in keeping with the criteria given in Chapter I. Therefore, the material has

Table 3. 996 hospitalized cases of chorea found in the archives of the clinics of Malmöhus county recorded after first visit (791) and return cases (205).

Hospital	Cases admitted		
	Total No.	First visit cases	Return cases
<i>Lund:</i>			
Ped. Clinic	220	173	47
Med. Clinic	123	101	22
Gyn. Clinic	20	8	12
Psych. Clinic	5	4	1
Rheumat. Clinic	2	2	0
<i>Malmö:</i>			
Flensb. Child. Hospital	7	6	1
Malmö Child. Hospital	146	114	32
Med. Clinic	168	137	31
Gyn. Clinic	8	4	4
Neurol. Clinic	8	7	1
Psych. Clinic	1	1	0
Epidemic Hospital	3	0	3
<i>Helsingborg:</i>			
Banck Child. Hospital	47	40	7
Med. Department	56	45	11
General Hospital	44	43	1
City Maternity and Gyn. Hosp.	0	0	0
<i>Hörby:</i>			
General Hospital	22	20	2
<i>Landskrona:</i>			
General Hospital	37	28	9
<i>Trelleborg:</i>			
General Hospital	45	33	12
<i>Ystad:</i>			
General Hospital	34	25	9
Total	996	791	205

been completed with anamnestic and catamnestic data through information by letter.

## 2. Compleutive Follow-up Examination.

The follow-up examination was carried out in June 1946 — February 1948 as follows:

From the total material (758 individuals) those patients are deducted who died in the hospital (13) and those whose address at the time of their hospitalization could not be obtained on going through the office archives of the hospitals (36). After this a questionnaire was sent to the remaining individuals (709) concerning previous or subsequent rheumatic manifestations, chorea occurring in the family, in cases of pregnancy, etc. Most of these questionnaires (611) were either returned as dead letters or remained unanswered, whereas 96 were filled in, and 2 individuals were reported to have died. Concerning the 611 individuals, through the kind assistance of the respective pastorates the present address was obtained for 449, while 96 were reported as dead, and in 66 cases the present address could not be furnished — owing to various circumstances, as a rule defective primary data. Then the questionnaire was sent to these 449 persons, of whom 381 returned it, properly answered, while 9 were reported to have died, whereas 59 have failed to respond in spite of the questionnaire being sent to them three times.

This compleutive follow-up examination divides the material as follows:

Number of persons in the material . . . . .	758	100%
Not to be found . . . . .	102	13.5%
Incomplete address . . . . .	93	
Entered only in the parish . . . . .	4	
Whereabouts unknown . . . . .	5	
No answer received . . . . .	59	7.8%
Dead . . . . .	120	15.8%
In the hospital . . . . .	13	
After discharge . . . . .	107	
Information by letter . . . . .	477	62.9%

Thus, concerning the 758 patients in the material, some information has been obtained about the subsequent course for 597 (79%), of whom 120 are dead.

As this material includes all the cases in which chorea has been diagnosed, even though it is recorded as dubious, all the respective case records have been gone through carefully as to whether chorea with certainty had been present during the hospitalization. This point was settled by means of the data in the case records and the information obtained through the compleutive follow-up examination. This «weeding out» has resulted in the exclusion of 54 patients

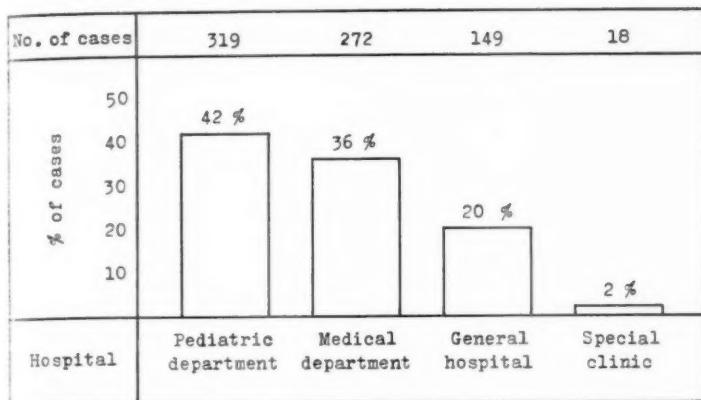


Fig. 2. Number and percental distribution of 758 persons with chorea at their first hospitalization in Malmöhus county 1910—1944 with regard to the kind of clinic.

in whom the chorea in the hospital was considered so dubious that they ought not to be entered in the chorea material. Therefore, the result of this is that the chorea material from Malmöhus county 1910—1944 includes 704 persons with unquestionable chorea. In the following this number is designated as the *main material*.<sup>1</sup>

### 3. Classification of the Material.

Every case in the main material (704) has been studied thoroughly with regard to the occurrence of the criteria given in Chapter I for rheumatic infection. Statements concerning any of these rheumatic manifestations in the case records for first admissions have been available for 343 patients, on readmissions for 43 patients; and the follow-up examination has shown that rheumatic manifestation has occurred prior to or after the first admission in additional 81 persons. Other rheumatic manifestations besides chorea are thus recorded for 467 persons and, in keeping with the nomenclature given in Chapter I, this group is designated as *rheumatic chorea*.

<sup>1</sup> Abstracts from the respective case records, together with information received by letter, including information about the cause of death, are available (in Swedish) in the University Library in Lund.

Among the remaining 237 cases there was sufficient reason to consider the chorea in 22 patients to have been due to some cause other than rheumatic infection. In the following this group is designated as *non-rheumatic chorea*.

This leaves 215 patients, concerning whom no data have been available as to the cause of their chorea, even though this may have been suggested in some cases. This group, therefore, is put down under the heading *cryptogenetic chorea*.

A survey of the classification of the material is given in Fig. 3, which also shows the percental distribution of the various groups in the material: rheumatic chorea 66%, non-rheumatic chorea 3% and cryptogenetic chorea 31%.

#### 4. Criticism and Appraisal of the Material.

The aim was to obtain a chorea material as representative as possible of the population of the Malmöhus county in 1910—1944. Owing to the aforementioned conditions for the collection of the material, however, this is not quite representative.

In the first place, those choreic persons are missing who were not treated in any clinic; and this applies also to persons belonging to this county but treated outside it. Further, there are the 30 hospitalized patients whose case records have been lost, as mentioned before. So the actual number of choreic patients in Malmöhus county in 1910—1944 is higher than given here.

Qualitatively too, the material is not complete. The observations taken into account here were made by various physicians in 20 hospitals during a period of 35 years. Owing to the number of examiners and the length of the examination period, the way of obtaining and recording the anamnestic data and the results of examination has not been altogether uniform — which also applies to the judgement of the examiners about the morbid state of the individual patients. In the task of evaluating the remarks put down in the case records, the writer has followed the rule: to rely more on an observation than on an estimate. Thus, if there is a discrepancy between an observation recorded and the diagnosis, the former is considered more likely. With discrepancy between the data in the case record and the information from the compleutive

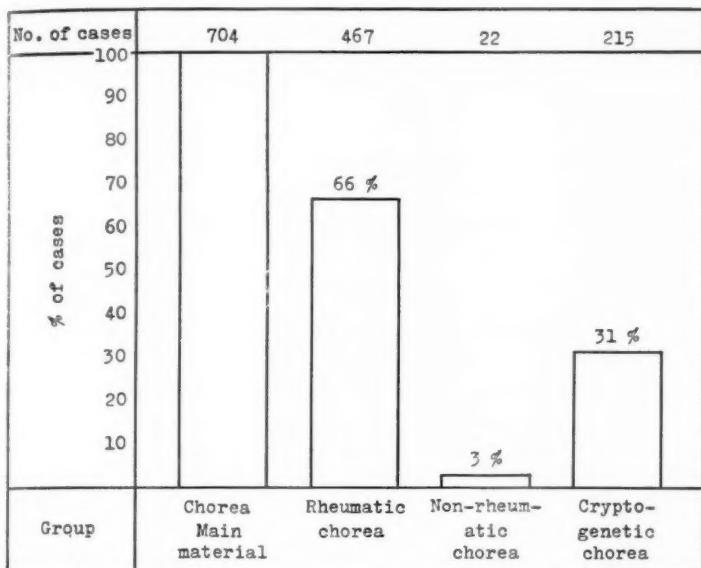


Fig. 3. Classification of 704 cases of chorea in Malmöhus county 1910—1944 with regard to the cause of chorea.

follow-up examination, naturally more reliance is put on the data of the case record.

Some of the shortcomings of the material are due to unavoidable factors. Often the choreic patient is a child who cannot by herself give the data of her history, past and present; and because of her movements, every choreic patient is difficult to examine. Moreover, chorea is such a relatively rare phenomenon that the experience of the individual diagnostician in this respect cannot become very wide. The outcome of the often incomplete examination is rendered even more difficult by the circumstance that some of the morbid conditions of which chorea is a symptom are lacking uniform criteria for an estimation — *e.g.* rheumatic infection and encephalitis.

The obtained information is to be evaluated in keeping with this knowledge. The figures arrived at are minimum figures, and the information obtained in most of the cases is merely approximate.

## CHAPTER III.

### Nomenclature of chorea.

#### 1. Introduction.

Chorea, a Greek-Latin word, signifies the act of dancing or dancing motility. It was introduced in the medical nomenclature from the religious cult in the Middle Ages, when dancing was one of the forms of its expression and, in that sense, without any pathological significance. The dancing motion, however, sometimes signified a morbid change in the motility and thus it came to signify a symptom of a disease.

There are but few medical concepts with a history extending so far back as chorea. For this reason alone it is difficult to survey. This is further accentuated by the circumstance that the nomenclature built up round chorea varies from time to time — and not always with historical, clinical or logical consistency. A feature particularly characteristic of the chorea nomenclature is that the very purport of the term chorea continuously has been variable, chorea being employed as the name of a disease and also as a term for a symptom or a symptom complex. On this account, down through the centuries we see almost every author on the subject trying to find the most proper use for the term chorea.

An example of this from the 18th century is found in Willman (1798) who commences the first scientific work on this subject in Sweden as follows: »Inter hoc occurrit morbi genus, quod *Scelotyrbe* quibusdam, pleurisque *Chorea Sancti Viti* audit. *Ballismus*, *Saltus Viti*, *Chorea Sancti Modesti*, *Choreomania & Epilepsia saltatoria*, nomina quoque sunt, quibus hunc morbum indicatum legimus. Chorea nomen eam maxime ob rationem ceteris praetuli, quod eodem usi fuerunt Sydenham, Cullen, Wichmann...».<sup>1</sup> An example,

<sup>1</sup> »This term is applied to a form of disease which sometimes is called *Scelotyrbe*, sometimes St. Vitus' chorea. *Ballismus*, *Saltus Viti*, *Chorea*

from the 19th century, is found in connection with the great discussion which in the 80's, especially in England, was kept up about the cause of chorea: »Again, discussion of chorea like that of ataxia, is in a measure complicated by the fact that the word is used in a double sense, to designate in man both a symptom and a disease or clinical type» (de Watteville, 1885). In our days, several authors try to get out of the dilemma by giving synonyms, thus, for instance, Miller (1933) writes: «Chorea. Synonyms: — Rheumatic chorea, Sydenham's chorea, chorea minor, St. Vitus's dance.»

Therefore, in order to understand the actual nomenclature of chorea it is essential to have some insight in the historical development of the chorea nomenclature and also to have some knowledge about the causes of chorea. It would not be practicable here to give a detailed account of these points concerning chorea in the different periods, and it will have to suffice here briefly to outline the development of the chorea nomenclature.

## 2. "Chorea" in the Literature down through the Ages.

### **From the Middle Ages to Sydenham (1686).**

In the introduction it was mentioned that in its original meaning chorea was not the name of a disease but of a symptom, the dancing motion. In the oldest medical nomenclature, too, the term was not merely the name of a disease. Its oldest nosographic designation is *S. Johannis chorea* (Höfler, 1899). Those who in the Middle Ages took part in the great dancing epidemics were considered suffering from this disease. St. John the Baptist was the patron saint against falling sickness, twitching and dizziness, besides against dancing mania — the last faculty because Salome's dance was paid for with the life of the Baptist. More recent investigation has made it probable that many of those who took part in the dancing epidemics were suffering from intoxication with ergot (Backman, 1945; and others).

After a dancing epidemic in Strassburg in 1418 we more fre-

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Sancti Modesti, Choromania and Epilepsia saltatoria are other names indicating this disease. The name of chorea seems preferable to the others, chiefly because Sydenham, Cullen and Wichmann have employed it . . .»

quently meet with the name of *St. Vitus' chorea* and its synonyms: *morbus S. Viti*, *saltus Viti* and *Saint Vitus' dance*, *dance of St. Vitus*, *Veitstanz*, *chorée de St. Vit*, *chorée de St. Guy*, and others. According to Wicke (1844), this name was found in a chronicle of Königshoven: »Viele hundert fingen zu Strasburg an, zu tanzen und zu springen, Frau und Mann, Am offenen Markt, Gassen und Strassen, Tag und Nacht ihrer viel nicht assen, Bis in das Wüthen wieder gelag. St. Veits Tanz ward genannt die Plag.»

Even in our days, both in the Anglo-American and in the German literature we often meet with the name of Vitus in connection with chorea.

According to the legend, a boy called Vitus died as a martyr in southern Italy during the Diocletian persecutions of the Christians in the beginning of the 4th century. His father tried to force him to renounce the Christian faith but not even when he locked him in with tempting dancing girls did he succeed in his heathen intent. Shortly before being put to death in a cauldron of boiling lead and pitch, Vitus is said to have prayed to God to preserve from the dancing mania all those who the evening before his day keep their fast and then celebrate his festival (15th of June). The legend tells that at once a voice was heard from heaven saying: »Vitus, thy prayer is accepted.» (Wicke, 1844; Bett, 1932).

Among the saints in the Roman Catholic Church, St. Vitus is one of «the helpers in need» with special power to help in St. Vitus' dance, falling sickness, rabies, snake bite and mania (Höfler, 1899).

St. Vitus' chorea was a heterogeneous group of lesions comprising all sorts of physical and mental diseases in which muscular motility constituted the only symptom and the name of which was stamped by the religious therapy. From this heterogeneous group Th. Sydenham, in 1686, isolated the »convulsiones species» through the following description, which is the foundation for the further development of the chorea nomenclature:

»... convulsiones est species, quae plurimum pueros puellasve a decimo aetatis anno, ad pubertatem usque invadit; primo se prodit claudicatione quadam vel potius instabilitate alterutrius cruris, quod aeger post se trahit fatuorum more, poste in manu ejusdem lateris cernitur; quam hoc modo affectus, vel pectori vel alii alicui parti adplicatam, nullo pacto potest continere in eodem situ vel horae momento, sed in alium situm aliquaque locum convulsione quadam distorquebitur, quidquid aeger contra nitatur. Si vas aliquod potu repletum in manus porrigitur, antequam illud ad os

possit adducere, mille gesticulationes, circulatorum instar exhibebit; cum enim poculum recta linea ori admovere nequeat, deducta a spasio manu, hue illuc aliquamdiu versat, donec tandem forte fortuna illud labiis proprius adponens, Liquorem derepente in os injicit, atque avide haurit, tanquam misellus id tantum cum ageret, ut dedita opera spectantibus risum moveret.<sup>1</sup>

Sydenham's authority was very great and his publications were widespread for that time, so that the picture of chorea he described became well known.

#### From Sydenham to Huntington (1875).

When Sydenham designated his »convulsiones species« by the earlier term *Chorea St. Viti*, he gave it a new and considerably more restricted purport, while at the same time the original meaning of this designation remained. Thus, while he brought about the great advance in the nosography of chorea, Sydenham also caused that confusion in the choreal nomenclature which still asserts itself. »We are both helped and handicapped in our knowledge of chorea by the work of Sydenham« (Swift, 1929). This confusion was also due in part to the fact that Sydenham failed to give a complete picture of the disease. As characteristics of his choreic picture, he gave a unilateral appearance of its manifestation and its occurrence in the age-class from 10 years to puberty; and he further failed to give any definite cause of the disease. So the question arose whether his description applies merely to a disturbance of the motility or to a disease. It seems that the common expression »a clinical unit« perhaps characterizes Sydenham's description most precisely.

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<sup>1</sup> »... a kind of convulsion which chiefly attacks children of both sexes, from ten to fourteen years of age. It first shows itself by a certain lameness, or rather unsteadiness of one leg, which the patient draws after him like an idiot, and afterwards affects the hand of the same side which, being brought to the breast, or any other part, cannot be held in the same posture a moment, but is distorted or snatch'd by a kind of convulsion into a different posture and place, notwithstanding all his efforts to the contrary. If a glass of liquor be put in his hand to drink, he uses a thousand odd gestures before he can get it to his mouth; for not being able to carry it in a strait line thereto, because his hand is drawn different ways by the convulsion, as soon as it has happily reached his lips, he throws it suddenly into his mouth, and drinks it very hastily, as if he only meant to divert the spectators« (cited after Bett, 1932).

The confusion resulting from Sydenham's description was greater in Germany than in England, because chorea St. Viti in the original sense of the term was more common in Germany than in England. This confusion, however, led on to efforts to straighten out the nomenclature, and as early as in the middle of the 18th century we find these efforts resulting in a new nomenclature. The chorea St. Vitus described by Sydenham was now designated as *Sydenham's chorea* or *Chorea anglorum*, a distinction in contrast to *Chorea germanorum* which would correspond to the original meaning of chorea St. Viti.

During the following century the definition and clinical meaning of the different concepts were discussed, above all in the German literature, and it was difficult to reach any agreement about them. The discussion was settled to some extent through Wichmann's (1827) »Ideen zur Diagnose» who suggested that »Veitstanz der Engländer» was to be looked upon as a milder form or modification of »Veitstanz der Deutschen». This view gradually gave rise to the designations *chorea magna* or *chorea major* for the »grosser Veitstanz» or *chorea germanorum* and *chorea minor* for the »kleiner Veitstanz», *chorea anglorum* or Sydenham's chorea.

But Wichmann's conception of Sydenham's chorea as a minor variant of the »grosser Veitstanz» met with strong opposition. An increasing number of authors emphasized that »kleiner Veitstanz» by no means is a variant of »grosser Veitstanz» but constitutes an entirely characteristic clinical entity. This view was set forth lucidly in Wicke's monograph (1844) »Monographie des grossen Veitstanzen und der unwillkürlichen Muskelbewegung», in which he suggests that the term »grosser Veitstanz» should be retained as the term for *chorea germanorum*, whereas he rejects the »kleiner Veitstanz» and suggests replacing this term with *unwillkürliche Muskelbewegung* — »... um schon die Idee zu verhüten, dass beide Krankheiten nur verschiedene Formen einer Krankheitsspecies seien».

While Wicke thus rejected the term »kleiner Veitstanz» he advocated that the epithet »gross» for »Veitstanz» should be preserved for the designation of *chorea germanorum* — with this motivation »... um ihn von dem, was sonst noch als V. bezeichnet wurde und wird, zu unterscheiden». As a matter of fact, after the middle of the 19th century the purport of »chorea magna» was reduced.

For, in the search for the cause of chorea magna, one group of symptoms after another could be distinguished and entered among well-known clinical entities. Finally, in 1877 v. Ziemssen was able to write the obituary of chorea magna. From then on, chorea magna merely belongs to the history of medical nomenclature.

The exitus of chorea magna was a result of the steadily increasing efforts in the 19th century to distinguish between disease and manifestation of disease, besides finding a cause for every disease or symptom. These efforts were made first and most strongly in France and a result of them is found also in the nomenclature of the chorea described by Sydenham. Thus, in his »Traité de la Chorée ou Danse de St. Guy», Bouteille (1810) — who was the first author to replace the term »danse de St. Guy» with »chorée» (Leroux, 1905) — proposes the following causal classification: *Chorée essentielle*, attacking children, especially between 10 and 14 years, and being due to inhibited development of puberty; *Chorée secondaire*, occurring at any age, complicated with or following some other disease, and *Chorée fausse*, which has nothing to do with chorea, merely resembling it.

The same basis of causal classification is found in the German literature on chorea, only somewhat later and somewhat modified — namely: *idiopathic chorea* in contrast to the sympathetic or *symptomatic chorea* — so that chorea thus may be both a disease and a symptom. In the course of the 19th century there is an increasing tendency to look upon the chorea described by Sydenham as corresponding to the essential chorea and the terms Chorea St. Viti, Sydenham's chorea, chorea minor and even chorea are reserved for the idiopathic form of chorea, which has been characterized most fittingly by Henoch (1895), stating that: »... die Chorea wie die Epilepsie überhaupt keine Krankheitseinheit, sondern nur eine Erscheinungsform ist, dass man daher am besten tätte, den Namen »Chorea» auf die bestimmte, mit wenigen Ausnahmen dem Kindesalter eigentümliche Neurose zu beschränken».

Furthermore, through the disappearance of chorea magna from the literature, the concept of chorea minor lost its relativity, and its employment became questionable. As Wollenberg (1899) says: »Was zunächst die Sydenham'sche Chorea oder Chorea minor betrifft, so muss die letztere Bezeichnung aufgegeben werden, weil sie ohne die Gegenüberstellung einer Chorea major sinnlos ist

und nur wieder verwirren kann». Towards the end of the 19th century, however, the attitude to the term chorea is stamped not only by an increasing confusion but even by a certain despair. Thus in 1885, in a discussion of chorea, Money says: »... with regard to the use of the expression »chorea«, I think we cannot substitute another term for chorea».

#### **From Huntington to Our Days.**

The further development of the chorea nomenclature is stamped, above all, by two things: Huntington's description of a new choreic picture, and the increasing prominence of the relation of chorea to rheumatic infection. On Long Island, George Huntington and his ancestors had observed a symptom complex in adults which was characterized by chorea, mental changes and heredity, taking a chronic and unfavorable course. This morbid picture had been described before but not as thoroughly and well as by George Huntington (1875), on which account it subsequently has often been designated as *Huntington's chorea*, thus emphasizing its contrast to Sydenham's chorea. Of other designations for this morbid condition mention may be made of chronic progressive chorea, chronic degenerative chorea and chronic hereditary chorea. This nomenclature has again had influence upon the nomenclature for the chorea described by Sydenham, resulting in terms as acute chorea, juvenile chorea and, not infrequently, infectious chorea (Wollenberg, 1899).

The term *infectious chorea*, however, has in some degree been employed to express the relation of chorea to rheumatic infection. Still, the knowledge that »rheumatism» may give rise to chorea has left its mark in the nomenclature at a considerably earlier date and in a somewhat different way. Thus Bouteille (1809) reported *chorée rhumatische* as a subgroup of chorée secondaire, Roger (1866) employs the term chorée rheumato-cardiaque. Bouteille's chorée rheumatique and Wollenberg's infectious chorea, however, are based on two different conceptions of the same cause of the rheumatic manifestation: in the beginning of the 19th century the clinicians spoke of rheumatic diathesis, towards the end of the 19th century they spoke of rheumatic infection.

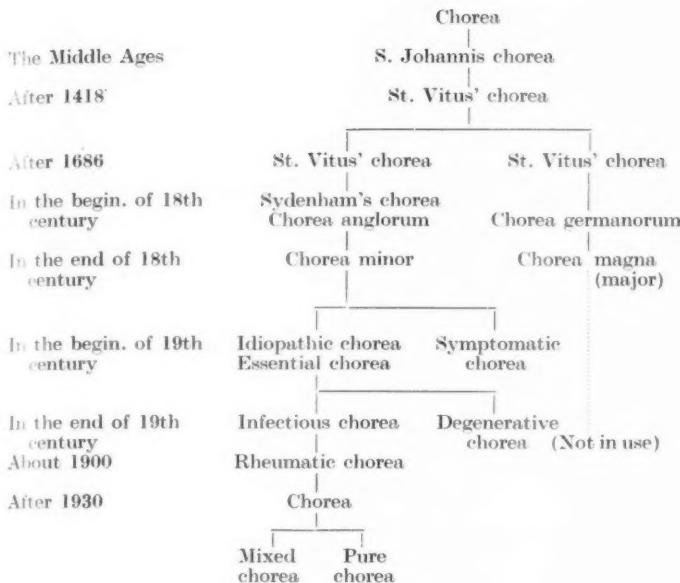


Fig. 4. A schematic survey of the more important features in the historical development of the chorea nomenclature.

Towards the end of the 19th century and in the beginning of the 20th century the interest taken in chorea chiefly concerned how often chorea occurred in connection with rheumatic manifestations as arthritis and carditis. Through close observation of choreic patients for a considerable length of time and through follow-up examination it was recognized that idiopathic chorea in most cases proved to be due to rheumatic infection, (e.g., Mackenzie, 1887; Osler, 1887; Donkin, 1893; Batten, 1898; Thayer, 1906). Therefore, it soon was assumed that the idiopathic chorea was due to rheumatic infection. This view was applied to the previous nomenclature and gradually more points of resemblance were established between Sydenham's chorea, chorea minor, idiopathic chorea and rheumatic chorea. In this way, then, the terms of Sydenham's chorea and chorea minor were also assigned an etiological purport.

In the beginning of the 20th century the chorea nomenclature yields to the dominance of the rheumatic infection. Especially in

the Anglo-American literature the term chorea is now seen not only to be deprived of its symptomatic purport and is employed to designate a disease, but also a definite etiological significance is attached to it: chorea is rheumatic chorea. In Parson & Berling's textbook, as mentioned in the beginning of this chapter, Miller (1933) wrote a chapter entitled »Chorea: Synonyms: Rheumatic chorea, Sydenham's chorea, Chorea minor, and St. Vitus's dance.» In his chapter, »Rheumatic chorea (Sydenham's chorea)» Walsbe (1945) says that »Chorea is an affection of the brain associated with rheumatic infection and characterized by...»; and Sheldon (1943) employs the following title: »Chorea (Rheumatic Chorea, Sydenham's Chorea, St. Vitus' Dance)» — just to mention some examples.

#### Recent Years.

The topical situation of chorea as reflected by the nomenclature just now is stamped partly by a somewhat vociferous tendency to let the nomenclature be formed entirely after the rheumatic etiology, partly by a more reticent tendency to retain chorea in the sense of a multivalent symptom, partly and chiefly by perplexity.

Thus the rheumatic view of chorea has given rise to the designation *pure chorea* for the form of chorea in which the rheumatic etiology cannot be made out. This term was employed first by Jones & Bland (1935) in a cautious way that does not exclude an etiology other than rheumatism. But the purport of pure chorea is shifting to mean rheumatic chorea without other rheumatic symptoms (Sutton & Dodge, 1938) and Usher (1938) uses a nomenclature based entirely on the rheumatic etiology. He also employs the term *mixed chorea*, and he states that mixed chorea is employed for »children who present the history of chorea but also have a history of other rheumatic manifestations» and that pure chorea is applied to »children who present a history of one or more attacks of uncomplicated chorea». This form of classification, however, has met with some criticism (Hedley, 1940).

Another example is found in McCulloch's (1938) suggestion instead of »chorea minor of Sydenham» to employ »the term *encephalitis rheumatica*... as proper and more descriptive. It should

serve to distinguish such cases from all others with a more obvious etiology or from those with idiopathic chorea of unknown etiology». He overlooks, however, the fact that rheumatic encephalitis may occur without any choreatic changes (Winkelmann & Eckel, 1932; v. Neergaard, 1934; Edström, 1937 and 1941), and that it is disputable whether rheumatic changes in the brain should be designated as encephalitis or as encephalopathy (*e.g.*, Lhermitte & Pagniez, 1930; Ford, 1946).

Further, the view that chorea is merely a symptom and that Sydenham's chorea and chorea minor are no clinical entity is not only of historical purport. After 1920 it has even been corroborated by the observation that the symptomatic picture of Sydenham's chorea or chorea minor may also be produced by endemic encephalitis. For it has been demonstrated that a clinical picture identical with monosymptomatic rheumatic chorea in its subsequent course turned out to be brought about by epidemic encephalitis, the cause being revealed by the postencephalitic state of the patients (Harvier & Levaditi, 1920; Sicard, 1921; Lesné & Baruk, 1924). The circumstance that no definite etiology may be established at the time of examination of a given case does not permit us to attribute the chorea to rheumatic infection — the cause may be an entirely different one.

But, in particular, confusion and perplexity characterize the modern chorea nomenclature, perhaps more than ever before. Weisenberg (1925) wishes to replace chorea minor, Sydenham's chorea and St. Vitus' chorea with a division into hysterical and infectious chorea. Critchley (1924) has given a very thorough description of chorea after diphtheria, but he employs the title: Post-diphtheritic »Chorea« — with chorea in quotation marks. The difficulty in getting along with the nomenclature is also evidenced from the work by Leichtentritt (1930) who speaks about »die Scheidung zwischen der echten Chorea minor, an deren rheumatischer Genese nicht zu zweifeln ist, und den Encephalitisfallen nach akuten Infektionskrankheiten«. Stefan (1940) gives his paper the title »Chorea minor infectiosa«, with the subtitle »Chorea minor Sydenham (Veitstanz)«. And Laestadius (1944) gives »chorea acuta« and »chorea rheumatica« as synonyms for »chorea minor Sydenham«. More examples could be cited from various authors, but the above

will suffice to illustrate the present situation of the chorea nomenclature.

It is to be mentioned, however, that sometimes we meet with a nomenclature built up in conformity with the literal purport of the term chorea, with historical tradition and with clinical experiences. Thus Wall (1920) thinks that we are justified in speaking of »rheumatic chorea» as a disease, and that we ought to employ the term »chorea» to indicate a symptom group, qualifying it in each case by an adjective indicating the supposed etiological factor. This suggestion, however, gave no particular results.

So, as yet there is no generally recognized chorea nomenclature, and every author has to state what he is talking about by employment of synonyms or circumlocutions.

### 3. "Chorea" in the Present Material.

The historical development of the chorea nomenclature and its current state as apparent from the literature invite us to take part in the practical adjustment of the chorea nomenclature in a clinical material. Not only the diagnostic variations are of interest, but also their relative occurrence and import.

The present chorea material ought to be able to illustrate these aspects. Several choreic features ought to be represented here, as this material comprises all cases diagnosed as chorea among the population of Malmöhus county. Because of its large size, thus, the material ought to be able to furnish representative figures for the frequency of the different diagnoses. As the material covers a long period it should be able in some degree to give a picture of the development of the chorea nomenclature. The diagnoses are made in various hospitals by different physicians, and this ought to contribute to the variegation of the picture.

A survey of the different diagnoses made in 704 first visit cases of chorea and the frequency of their employment are given in Table 4. A conspicuous feature is the great number of diagnoses that have been employed — no less than 17 different diagnoses.

Among these diagnoses, chorea and chorea minor predominate, being applied to 326 and 317 cases respectively. Added together, the two diagnoses have been employed in 643 or 91% of all the

Table 4. Distribution of various diagnoses on 704 cases of chorea,  
together with variants of diagnoses.

Diagnosis	No. of cases	Variants
Chorea	326	Chorea (postencephalitic?) Encephalitis? Chorea? Epilepsy? Encephalitis (chorea, almost hemiballism) Chorea (psychosis) Chorea (hysteria?) Hysteria magna (chorea?) Chorea (psychogenetic symptom in debility?) Psychosis from infection (chorea) Chorea (pavor nocturnus)
Chorea minor	317	Chorea minor (acute encephalitis) " " (lethargic encephalitis?) " " recurrent with psychosis " " " (mollis) " " (hysterical?)
Hemichorea	15	Hemichorea minor, hemichorea paralytica " syphilis III? " (lethargic enceph.? Tumor of brain?)
Chorea gravidarum	11	Chorea gravidarum levis " (gravidarum?) " (chron.) gravidarum
Huntington's chorea	9	Chronic hereditary chorea (Huntington)
Chorea levis	7	
" gravior	1	
" gravis	3	
Rheumatic chorea	5	Rheumatic fever with chorea?
Sydenham's "	3	
Infantile "	1	
Acute chorea gravis	1	
Chorea in pregnancy	1	
" nongravid.	1	
" magna	1	
Microchorea	1	
Arteriosclerosis with chorea	1	

Table 5. Occurrence in 5-year periods of the diagnosis chorea minor in 317 first visit cases of chorea in Malmöhus county 1910—1944, with reference to the presence or absence of rheumatic infection.

Year	Total	Diagnosis: Chorea minor	
		Rheumatic infection	No rheumatic infection
1910—1914	58	35	23
1915—1919	29	18	11
1920—1924	41	28	13
1925—1929	41	36	5
1930—1934	81	48	33
1935—1939	38	28	10
1940—1944	29	17	12
Total	317	210	107

cases. The diagnoses next in frequency are: hemichorea (15 cases), chorea gravidarum (11 cases), and Huntington's chorea (9 cases). The term »chorea» has not been employed consistently to designate any symptom or disease. As a rule, it is true, »chorea» has been used to designate a disease, but the employment of »chorea» to designate a symptom is evident from the diagnoses: rheumatic fever with chorea and arteriosclerosis with chorea. To what extent a symptom or a disease is implied in the 326 »chorea» diagnoses cannot be decided.

We know that, according to the criteria adopted for the present material, rheumatic infection has positively been the cause of chorea in 467 cases. But this etiology is evident from the diagnosis only in 5 cases. On going through the chorea literature, it will be noticed that in our days there is a tendency to attach an etiological import to the »chorea minor» and »chorea» diagnoses, to let them designate chorea of rheumatic etiology. Likewise it has been pointed out that for every year there is an increasing tendency to employ »chorea» to designate a disease: »chorea» is chorea in rheumatic infection.

It may be of interest, therefore, in our material to look for the answers to the following questions:

Table 6. Occurrence in 5-year periods of the diagnosis chorea in 326 first visit cases of chorea in Malmöhus county 1910—1944, with reference to the presence or absence of rheumatic infection.

Year	Total	Diagnosis: Chorea	
		Rheumatic infection	No rheumatic infection
1910—1914	86	37	49
1915—1919	59	21	38
1920—1924	65	34	31
1925—1929	58	34	24
1930—1934	21	5	16
1935—1939	16	7	9
1940—1944	21	12	9
Total	326	150	176

- I. Do the diagnoses »chorea minor» and »chorea» imply a rheumatic etiology?
- II. If so, what is the »rheumatic value» of these diagnoses?
- III. Does the present material show an increasing tendency to employ »chorea» as diagnosis of rheumatic disease with chorea?

The answers to these questions are found in Tables 5 and 6, which were obtained by studying the anamnesis, clinical condition and diagnosis in each of the 643 cases concerned, 317 cases of chorea minor and 326 of chorea. In judging as to whether a rheumatic etiology has been present in the individual cases, of course, the data obtained through the compleutive follow-up examinations are not made use of here, as they were not at the disposal of the original diagnosticians.

As was to be expected, the answer to question I is in the affirmative. A rheumatic etiology was positively present in 210 cases of chorea minor and in 150 cases of chorea. These figures also suggest strongly that a rheumatic etiology might not have been present in all the cases. Thus, neither diagnosis means invariably a rheumatic etiology, merely the possibility of a rheumatic etiology.

A comparative estimate of how often a diagnosis implies a rheumatic etiology is here designated by the »rheumatic value»

of the diagnosis, and a numerical expression of this «value» is obtained in the proportion between the number of cases with rheumatic etiology and the number of cases of other or unknown etiology registered under the same diagnosis. In this way, chorea minor is found to have a rheumatic etiology in 210 out of 317 cases (66%), chorea only in 150 out of 326 cases (46%). The figures in this material may be said to show that a rheumatic etiology may have been present both in cases of chorea minor and in chorea, though more often under the former diagnosis — *i.e.*, «chorea minor» has greater rheumatic value than «chorea».

The question whether the present material in the later years shows an increased tendency to employ chorea as diagnosis of rheumatic disease with chorea may be answered by examining how often «chorea» implies a rheumatic etiology in the period of 1910—1924 in comparison to the period of 1930—1944. In this way we find that a rheumatic etiology was ascertained in 92 out of 210 cases (44%) in the first period, and in 24 out of 58 cases (41%) in the latter period. As in the entire group of «chorea» and «chorea minor» a rheumatic infection was ascertained in 173 out of 339 cases (51%) in the first period, and in 117 out of 206 cases (57%) in the latter period, it is evident that the tendency apparent in the literature increasingly to employ «chorea» to designate a rheumatic lesion is not noticeable in the present material.

The question now may be raised whether the confusion in the chorea nomenclature as observed in the literature may be found also in the present material. Undoubtedly it seems justified to take the great number of diagnoses listed in Table 4 as an example of the difficulty in establishing and maintaining the chorea nomenclature. If then we look for some uniform systematic adjustment of the nomenclature in the present material we find that this has been attempted but exceptionally. The causal nomenclature desirable in all nosography — *cf.*, for instance, Standard Nomenclature of Disease by The American Medical Association, 1947 — has been adapted only in 6 out of the 704 cases in our material: in 5 cases the diagnosis indicates that rheumatic infection is the cause of the chorea, while in 1 case arteriosclerosis is taken to be the cause. An attempt at a systematic diagnosis other than the causal may be found in «chorea magna» and «microchorea» in contrast to «chorea minor», also in «chorea levis, gravis and gravior» and in

»chorea in pregnancy» in contrast to »chorea nongravidarum». But no general systematic diagnostics may be found in our material. Undoubtedly, then, the diagnostic variations listed in Table 4 give a fairly good expression of the difficulty of the diagnostician in his application of the chorea nomenclature.

#### 4. Discussion and Conclusion.

The chorea nomenclature employed in the present material may be said very well to illustrate the nomenclature encountered in the recent chorea literature. It is variegated, lacking any definite principles, and its application is rather confusing.

A uniform nomenclature is required, and this want is urgent. The prevailing habit of letting »chorea» imply a rheumatic disease exclusively is unfortunate, as the appearance of chorea may signify various causal factors.

In the literature — and in the present material too — there is a noticeable tendency to formulate *a nomenclature according to the causal factor* in the appearance of the choreic phenomenon. This tendency is far from pronounced yet, it is true, but it is in keeping with medical systematics in general.

The terms St. Vitus' chorea, Sydenham's chorea and chorea minor are not causal ones, and attempts to make them causal concepts have only failed; furthermore, on employment of a causal nomenclature they will be entirely superfluous. It is time for them to take their place in the history of the medical nomenclature alongside »chorea magna».

A causal nomenclature, however, requires knowledge of the various causes of chorea and their appraisal. A review of the etiology in chorea will be given in the next chapter.

## CHAPTER IV.

### Etiology of chorea.

#### 1. Introduction.

In Chapter I it was mentioned that chorea *per se* says nothing about the etiology of the lesion, as it is the pathophysiology of the choreatic system, not the character of the injury, that forms the symptom. Still, the clinical milieu of a given case of chorea may offer some suggestion as to the cause of the affection.

Down through the times, thus, the clinicians have gathered their observations round chorea, and clinical empirics have made it possible for us in many cases to give the cause of the chorea. In exceptional cases, pathologic anatomy and bacteriology or serology have contributed to our etiological knowledge. Experimental research, tried by several authors, has not offered any particular contribution concerning the etiology of chorea, chiefly because it is questionable whether chorea may be produced at all in animals (Ingvar, 1934; Collis, 1937). Our knowledge about the cause of chorea, therefore, is incomplete and not solidly founded. Finally, the border-line between what we believe we know and what we know — between hypothesis and fact — is often difficult to draw in this field.

The connection of chorea with »Rheumatismus« was observed already in the latter part of the eighteenth century, and now we know rheumatic infection to be looked upon as the most common cause of chorea. In comparison to other causes it is so common that now and then we fail to keep in mind the possibility of the other causes. Through its dominance, rheumatic infection puts its stamp on our conception of the etiology of chorea, on which account the present material etiologically is classified as follows:

Rheumatic chorea . . . .	467 cases
Non-rheumatic chorea . .	22 »
Cryptogenetic chorea . .	215 »

The literature has indeed brought numerous reports on various causes of chorea, and the number of such causes increases the farther back we delve into the literature. Neither quantitatively nor qualitatively is the available material proportional to the observations and experiences reported. Here it has been used chiefly to illustrate the occurrence of different causes of chorea. In our material, however, not all causes of chorea are represented — in such cases only a review of the appertaining literature is given.

## 2. Rheumatic Chorea.

### Clinical Aspects.

The prevailing idea about chorea being associated with rheumatic infection is based chiefly on observations on the patients. Our present knowledge is the product of many single observations and their correlation. The comprehensive literature on the lesion shows that this knowledge could be acquired only through a lot of troublesome and painstaking work. The clinical picture of the rheumatic infection has always been difficult to define, and it has been developing continually.

Max Stoll is looked upon as the first author to assert a relation between rheumatic *arthritis* and *chorea*, when in 1780 he reported two cases of rheumatic trouble and chorea. One of these patients was a girl of 16 years in whom chorea developed on the second day after the onset of a fever with rheumatic pains in the right arm; the other was a girl who »avait eu d'abord un rhumatisme fort long qui fut négligé et qui finit par dégénérer en danse de Saint-Witt» (cited after Roger 1866). Wöltge (1783) mentioned a case of chorea with »Rheumatismus beider Knieve», and Salt (1793) suggests that the rheumatic affection of the extremities may even be the cause of chorea. As early as 1803 Barthez, in a dissertation on diseases of the joints, set up a group which he called Chorea arthritica.

In the middle of the nineteenth century several large collations were published on observations concerning chorea and »rheumatismus» in the same patient (*e.g.*, Todd, 1843; Hughes, 1846; Sée, 1850; Hughes & Brown, 1855). Among these works, particular mention is to be made of the investigation carried out by Sée, as it explains

many of the features of chorea and rheumatic infection that later have been the subject of investigations. Thus, Sée reported that among 11,500 sick children he found 109 with «rheumatismus», and among these 61 had chorea. He observed three different situations in the appearance of chorea: in the first case, chorea is preceded by rheumatism, which is the most common sequence; in the next case, chorea and rheumatism are coincident, or chorea is followed by rheumatism; in the third case, chorea is complicated by rheumatic manifestations which do not involve the joints, namely: endocarditis and pericarditis. Sée was ahead of his time in his conception of the rheumatic diseases. »Er brachte den Begriff der «rheumatischen Diathese» in die Lehre der Chorea hinein», as Kroner (1896) says. But he was not the first to point out the connection between arthritis and chorea.

With the publication of these large British and French investigations concerning the relation of chorea to rheumatic infection it was proved that there is a clinical connection between chorea and arthritis. A few objections were raised (e.g., Steiner, 1872; Prior, 1886), but the observations from the middle of the nineteenth century still hold true.

The connection between *chorea and carditis* was elucidated almost simultaneously with the entry of the carditis among the rheumatic manifestations. In his »Cases of Spasmodic Diseases Accompanying Affections of the Pericardium», Bright (1839) pointed out the connection between chorea and endocarditis and pericarditis. According to Duckworth (1885), as early as before 1850 Addison emphasized the connection between chorea and cardiac disease, and in the works published by Hughes (1846), Sée (1850) and Roth (1850) we find this connection emphasized. Roth even employed the term »chorée rheumo-cardiaque» to designate the etiological connection. But it was the French pediatrician Roger (1866) who turned the connection between the three manifestations — arthritis, chorea and carditis — into a general medical concept. In his »Recherches cliniques sur la chorée, sur le rhumatisme et sur les maladies du coeur chez les enfants», Roger exclaims quite enthusiastically: »Ici, l'identité est flagrante: la maladie des articulations, la chorée, la phlegmasie cardiaque, se mêlant, se remplaçant, se confondant de nouveau, ayant même origine et même fin, ne sont-elles pas la triple expression d'un vice unique, le vice rhumatis-

mal?» In the sixties »the embolic theory of chorea« was advanced (Kirkes, 1863; Jackson, 1867), which claimed that chorea was caused by small emboli from the rheumatic process in the heart being carried by the blood stream through the middle cerebral artery to ganglia in the midbrain. But this theory was not tenable, neither clinically nor pathologic-anatomically, and as an etiological explanation of rheumatic chorea it was discarded long ago. But it illustrates how easily explainable the connection between chorea and carditis once was taken to be, whereas now we can merely ascertain a connection, not explain it.

When, in their classical description of subcutaneous nodules, Barlow & Warner (1881) entered these structures in the rheumatic picture, the connection between *chorea and nodules* was also emphasized at the same time: »With regard to chorea ten of our patients were the subjects of this neurosis under our observations ...». The authors emphasize that subcutaneous nodules in some cases may help to establish the relationship with rheumatism. The brief description given by Barlow & Warner is so comprehensive and correct that as to the connection between chorea and nodules nothing fundamentally new has been added since their days. As a matter of fact, nodules are a rare phenomenon, and the coincidence of chorea and nodules in the same individual is even more infrequent.

*Erythema annulare* as well as *tuberculin-negative erythema nodosum* hardly ever constitute the only rheumatic milieu of chorea. Lehn-dorff & Leiner (1922) thought that *erythema annulare* does not occur without the presence of endocarditis. They also reported that they had observed the typical skin changes in patients with chorea.

Since the *clinical* connection between chorea and the other rheumatic manifestations was established, in the literature we meet with many works aiming to give in exact figures how often the different manifestations make their appearance. The figures given represent merely the authors' own materials. For, the epidemiology of the rheumatic infection is so varying, the picture of the rheumatic infection in different age classes so changing, and the conception of the diagnosis of the rheumatic manifestations so individual that two quite comparable materials are not to be found. Here it will suffice to give the figures reported by Pfaundler & v. Seth (1921). They employed the term »Syntropie« for a »Sich-

gegenseitigzuwenden oder -zuneigen zweier Krankheitszustände, and graded this property by means of a »syntropic index». They observed 28,090 cases of various diseases in the pediatric clinic in Munich, 1906—1920, and found a syntropic index of 34.73 for Chorea-Vitium-cordis, 12.94 for Chorea-Gelenkrheumatismus, and the highest index of all, 58.55, for Gelenkrheumatismus-Vitium cordis. The syntropy for the triad Gelenkrheumatismus-Vitium cordis-Chorea minor was the highest for all triads.

In this connection, however, the most important question is not about the degree of syntropy but decidedly about the extent to which the clinical connection signifies an *etiological* connection. As already mentioned, we have no routine test for rheumatic infection, which otherwise might indicate when a symptom or symptom complex is of rheumatic etiology.

The blood sedimentation rate is generally looked upon as our most sensitive index of rheumatic infection, an active rheumatic infection being taken to give an increase in the sedimentation rate. It is a common medical experience, however, that the sedimentation rate often is normal in chorea (e.g., Hill, 1932; Hässler & Möller, 1932; Struthers & Bacal, 1933; Gerstley *et al.*, 1935; Jones & Bland, 1935; Coburn & Moore, 1937; Usher, 1938; Edgren, 1938; Jacobsson, 1946). Further, a rise in the sedimentation rate in chorea is generally taken as a rule to indicate another rheumatic manifestation. The low sedimentation rate in chorea has even made several of the above-mentioned authors question chorea as a rheumatic manifestation. Coburn & Moore (1937) assert that chorea with a normal sedimentation rate, anyhow, cannot be taken as a sign of rheumatic activity.

With regard to the above statements about a normal sedimentation rate in chorea, in the present material the writer has not employed the sedimentation rate as a criterion of rheumatic infection, employing only the clinical manifestations for this purpose. In this way the character of the material as expression of rheumatic infection becomes indisputable from a clinical point of view. Furthermore, in this way the writer is also enabled through studies on an unquestionably rheumatic material to elucidate the behavior of the sedimentation rate in rheumatic chorea.

Thus, in the absence of any specific test for rheumatic infection, it is not possible for us clinically to answer the question whether

the clinical connection observed between chorea and the mentioned rheumatic manifestations also is an etiologic connection. So we have to look for the answer in the pathologic anatomy or bacteriology.

### Pathologic Anatomy.

In the pathologic anatomy the first explanation of the connection between chorea and heart lesion was found in the aforementioned »embolic theory of chorea«, which attributed the chorea to the small emboli in the middle cerebral artery from the rheumatic endocarditis. If the ganglia were destroyed, paralysis was the result; if only their function was disturbed, chorea was the result. Kirkes' theory led Money (1885) to try experimentally to produce chorea by injection of »arrowroot particles, granules of potato starch and carmine« into the common carotid artery on rabbits, guinea-pigs, cats, and dogs; and he obtained movements which he designated as choreatic. Kirkes' theory, however, met with the objection from pathologic anatomists that embolism was absent in most cases of fatal chorea occurring in children (Sturges, 1888). In our days this theory is mostly of historical interest, but it has been of great significance to our conception of the localization of the changes giving rise to chorea.

In the latter part of the nineteenth century descriptions were given of the tissue changes which through Aschoff's account in 1904 became recognized as characteristic structures of rheumatic nature; and since, they usually are designated as Aschoff submiliary nodules. As to the genesis of the initial changes and the significance of the microscopic changes, opinions are divergent. The specificity of the changes may be disputed; Aschoff (1939) himself considers »the cell formations specific to, and exclusively seen in the Bouillaud-Gräff disease«. Pathologists and clinicians agree that the Aschoff nodule is the tissue change most specific of rheumatic infection. Other tissue changes — fibrinoid degeneration, endothelial proliferation in arterioles and capillaries — are described as typical of rheumatic infection, but the specificity is strongly disputed. Aschoff's observation of his granulomas, which as a rule are situated perivascularly, has brought about that the rheumatic infection is taken to be a disease limited to mesenchymal tissues.

One might have expected the specific rheumatic tissue changes to contribute to an explanation of the connection between rheumatic infection and chorea. Some pathologic-anatomical observations have been made in chorea, but their interpretation is still unsettled. It will be appropriate here to mention some of them that have attracted most interest.

Alzheimer (1911) finds changes in rheumatic chorea in the subthalamic region and in the corpus striatum, consisting in small, mostly perivascular, foci of glia, here and there with staff cell-like elements.

Greenfield & Wolfsohn (1922) report the findings in a girl, 7 years old, who died with features of acute chorea, after 10 days of illness. The heart was enlarged, with vegetations on the valves. Thrombi were found in some cerebral vessels with small-cell infiltrations near by, endothelial proliferation in the capillaries and emigrated round-cells in the surroundings. The authors arrived at the following conclusion: «There is now a sufficient body of evidence to prove that the pathological basis of chorea minor is a diffuse or disseminated encephalitis affecting chiefly the corpus striatum and involving the cortex and the pia arachnoid. It seems more than probable that the microorganism responsible for this encephalitis is the same as that which causes the carditis and arthritis of rheumatism. The lesions have been most constantly found in the caudate nucleus and the putamen ...»

In a boy, 10 years old, who died with chorea on the tenth day of illness, Marie, Bouttier & Tretiakoff (1923) found inflammatory changes in the cerebral cortex and corpus striatum, with hyperemia and infiltration with leukocytic elements and glia cells.

Lewy (1923) examined 11 cases of infectious chorea and found in most of them only degenerative changes, most pronounced in the neostriatum, especially in the small striatum cells. He found no regressive increase in glia and, as a rule, no vascular changes in the acute cases.

Wilson & Winkelmann (1923) describe a case of chorea in a girl, 12 years old, with endocarditis. Autopsy showed vegetations on the mitral valve, but thorough examination of the brain, especially of the basal ganglia, showed no specific changes.

Castré (1925) examined the body of a woman, 23 years old, who died after nearly 4 weeks' illness with chorea. The heart showed vegetations on the mitral and aortic valves. He found hyperemia, hemorrhages, thromboses, and areas of necrosis, but also regressive changes, increase in the glia round the vessels and ganglion cells. He emphasizes the diffuse extension of the lesion, and he thinks that for differentiation between epidemic encephalitis and «acute (Sydenham) chorea» one will have to rely on the endocarditic changes in the heart.

Lhermitte & Pagniez (1930) examined the brain from a girl who had shown choreatic movements for a couple of months. They found vascular and cellular changes on which account they ventilate the possibility of exclusively degenerative changes in chorea.

In view of these and other studies, Schröder (1931) thinks that »Knötchen, welche vermutlich als Analoga der von Aschoff gefundenen in Muskulatur und Gelenkwänden anzusehen sind, hat bei rh. Chorea bereits Alzheimer 1911 besonders in Corpus striatum und in der Regio subthalamica beschrieben ...» Goebel (1938) holds that »Die Zugehörigkeit der Chorea minor zum Rheumatismus als eine dem Kindesalter eigentümliche Lokalisation der spezifischen Gewebsreaktion, des Knötchens, in bestimmten Gebieten des Hirnstamms, besonders des Corpus striatum, kann heute auch anatomisch als gesichert angesehen werden.» v. Müller (1931) mentions the changes observed in rheumatic chorea and arrives at the conclusion: »Eigentliche rheumatische Knötchen oder auch Bakterien konnten dabei nicht nachgewiesen werden.» Reviewing the pathologic-anatomical investigations reported, in particular that by Lenz (1931), Klinge (1933) says: »Irgend etwas den rheumatischen Knötchen im Herzen etwa Vergleichbares fehlt im Gehirn.» Discussing the pathologic-anatomical changes, Winkelman (1947) says: »... that acute rheumatic fever does not produce a specific change in the brain that can be recognized either grossly or microscopically (edema, endarteritis of the small vessels, acellular areas).» Finally, in the last summarizing description of the pathologic-anatomical findings to be mentioned here — namely, the review given by v. Glahn (1947) — no changes specific of rheumatic infection are ascertained in chorea.

Previously, Swift (1929) had emphasized that the very small amount of mesenchymal supporting tissue in the brain probably explains in part the difference in microscopic picture between choreic and other rheumatic lesion. And recently Coburn (1945) puts chorea as pathologic-anatomical problem in its proper place, saying: »Many manifestations of rheumatic fever, such as chorea, represent physiologic changes which cannot be studied in the microscope.»

No pathologic-anatomical examination of the present chorea material has been made, and the proper interpretation of the above-mentioned examinations will have to be left to the pathologists. In view of the above opinions, however, the writer ventures to conclude that also pathologic-anatomically it has been impracticable with certainty to show any definite etiologic connection between chorea and rheumatic infection.

### Bacteriology.

The first theory about chorea being of infectious origin was advanced by P. Koch (1887), who assumed the existence of a specific choreal virus the entry of which into the organism was promoted by other infectious diseases, above all, »polyarthritis rheumatica». Or »das rheumatische Virus» was near-related to the choreal virus and possibly able by itself to produce chorea.

Wollenberg (1899) advocated the view »dass der Zusammenhang zwischen Chorea und rheumatischer Infection ein mehr mittelbarer ist, insofern es sich nicht um die Wirkung der betreffenden Mikroben selbst, sondern um ihr im Blute kreisenden Stoffwechselprodukte handelt ...». Also other infections may possess choreogenic properties. »Offenbar muss aber das rheumatische Virus die choreogenen Eigenschaften in ganz besonders hervorragendem Masse besitzen». He discusses also the possibility of a toxic effect on the brain in analogy to the findings in diphtheria.

Westphal, Wassermann & Malkoff (1899) ushered in the present streptococcal era of the bacteriology in chorea through their finding of streptococci in a case of polyarthritis, endocarditis and chorea. A few years later, Poynton & Holmes (1906) reported three cases of chorea, in which a diplococcus was found in the pia mater and they concluded »that chorea is a manifestation of acute rheumatism and that the Diplococcus rheumaticus is the infective agent in acute rheumatism». Their finding, however, has not been confirmed yet.

Quigley (1918) isolated streptococci from the blood and cerebrospinal fluid of choreic patients and attempted in animal experiments to show that the streptococci were the cause of the chorea — though without success. He thought that the streptococci still were of significance to the development of chorea.

Rosenow (1923) reported that he had isolated streptococci from the nasopharynx and tonsils in a patient with chorea. He injected these bacteria into the cranial cavity and dental alveoli on rabbits, and he was able to produce a disease »much resembling chorea». He even produced a serum which specifically agglutinated the bacteria he had isolated. On this account, Gerstly & Wilhelmi (1927) tested a serum produced »by the use of the Rosenow chorea streptococcus» on every other of 27 choreic patients. In all the children who were given this serum the disease took practically the same course as in the controls. Gerstley & Wilhelmi concluded »that the organisms we obtained from cultures of the nasopharynx were not the true organism of chorea.»

Harvier & Levaditi (1920) find that acute febrile chorea in some cases is due to the virus of epidemic encephalitis, and they hold that possibly

Sydenham's chorea in children in certain cases is ascribable to the virus of epidemic encephalitis. This led Babonneix (1923) to publish a paper entitled «La chorée de Sydenham doit-elle être considérée comme une "provinces de l'encéphalite léthargique?"», in which he establishes that Sydenham's chorea has nothing to do with lethargic encephalitis.

This short survey of the findings reported and hypotheses advanced concerning the bacteriology of chorea may properly be concluded with a quotation from Poynton & Schlesinger (1937) who sum up the situation as it still is today: »Even the strongest advocates of a streptococcal cause of rheumatism favour the view that chorea is very likely due to a circulatory bacterial toxin. Others suggest that the nature of the inflammation of the cerebral tissues is chemical rather than bacterial. Finally, although there is as yet no proof, the conception of a virus as the cause of chorea has much in its favour and would explain many of the clinical and pathological anomalies of this particular manifestation of rheumatism.»

As yet, however, it has not been possible bacteriologically to prove that the clinical connection between chorea and rheumatic infection also implies an etiological connection.

#### **Analysis of the Material.**

The rheumatic chorea material comprises 467 patients, 150 male and 317 female. All these patients fulfil the criteria of rheumatic infection as given in Chapter I.

By adjusting these criteria the writer has taken his stand from the start in the discussion about the rheumatic etiology of chorea, namely: a rheumatic etiology is present when these criteria are fulfilled. Rheumatic infection becomes a clinical concept, and the diagnosis rheumatic chorea is given when the case complies with certain clinical rules. The cause of chorea thus becomes dependent on medical tradition. This holds true of the diagnosis in most cases of rheumatic affections, and realizing that as yet we are wanting the means for an objective and positively correct diagnosis of rheumatic infection, it has to be so.

Therefore, the material taken as a whole cannot contribute to solve the etiological problem whether or not rheumatic infection is the true cause of chorea; it can merely illustrate how the matter stands when rheumatic infection — after the given rules — is

present in chorea. The capacity of the material in this respect, however, depends primarily on the notes put down in the case records, secondarily on the interpretation of the given data.

Information in the *anamnesis* about manifestations of rheumatic infection other than chorea is given in 309 case records: positive data in 235 cases, dubious or negative in 74.

Notes concerning previous arthritis are found in 248 case records. In 62 of these cases there was no joint complaint whatever, while 186 (73%) had had joint complaints, and 81 of the latter had also had swelling of joints.

In 37 case records it says that on previous hospitalization or other medical examination the patient had been told he had a heart lesion. In 3 cases subcutaneous nodules were observed already before the present admission.

In the 467 case records notes are found about observation *on admission or later* of rheumatic manifestations other than chorea in 433 cases. In 34 cases — all from the first years of the period here concerned — no note is made of such observations.

The presence of carditis is recorded in 294 cases; in the remaining 139 cases no sign of heart lesion could be found. This means that, with the examining technique employed, the presence of carditis could be ascertained in 68% of the cases observed with regard to this complication. (In the entire material from 1910 to 1944, X-ray examination of the heart was performed only in 28 cases, electrocardiography in 65.)

Notes on examination of the patient with reference to involvement of joints are found in 91 cases. Positive findings are recorded in 31: tenderness of joints in 14, tenderness and capsular swelling in 8, capsular swelling alone in 9. These figures tell us that objective signs of arthritis on admission or under treatment for rheumatic infection with chorea were present in 34% of the patients under observation in this respect.

Subcutaneous nodules are recorded in 2 cases, erythema annulare in one, whereas no instance of tuberculin-negative erythema nodosum + chorea appears to have been present.

The above figures from the anamnestic notes and from the stay in the hospital show that arthritis is the most common observation in the anamnesis, carditis the most common in the hospital, and that both occur with about the same relative frequency.

Of the 467 patients 81 could be recorded as rheumatic chorea only after the *completive examination*. For an analysis of the questionaries returned shows that 25 patients had arthritis before or during their hospitalization, 22 after, *i.e.*, altogether 47. On account of cardiac disease, 33 patients are put down as rheumatic. Now 19 of them are known to have died under the diagnosis cardiac disease, valvulitis or pericarditis. Of these 19 patients, 2 died during the first year after their hospitalization for cryptogenetic chorea, 10 during the first decade after, 5 during the second, 1 during the third, and the remaining 3 during the fourth decade. One patient (Case 344), who was first under hospital treatment for chorea in 1940, has had several relapses of chorea, »and each time accompanied by a lot of hard lumps on the back of the skull — as big as beans, from ten to twenty of them». Undoubtedly this is an instance of subcutaneous nodules, and his previous cryptogenetic chorea is therefore now entered under rheumatic chorea.

The material was not planned from the start to be worked up scientifically, and therefore it is not serviceable for a detailed study of the rheumatic manifestations. Still, it was deemed of considerable interest to investigate the *sedimentation rate* in this material where rheumatic infection was considered present when chorea and some other manifestation (arthritis, carditis, subcutaneous nodules) appeared in the same patient. So the sedimentation rates recorded on admission to the hospital in such cases are picked out and classified; and the result is evident from Table 7.

Examination of the sedimentation rate is recorded for most of the cases after 1927 — altogether 150. In some cases the value obtained by the sedimentation test ad modum Landau is given in the case record. Such values are converted to sedimentation rate after Westergren before they are tabulated. As will be noticed, a rate between 0 and 10 was obtained in 67 cases (45%). This figure shows that there was no increase in the sedimentation rate in nearly half of the cases diagnosed on the aforementioned criteria as rheumatic chorea. How the sedimentation rate may behave in the individual cases is illustrated by the following two cases from different age-classes:

Table 7. Sedimentation rate (ad modum Westergren) in 150 first visit cases of rheumatic chorea, first sedimentation test on admission to hospital.

S. R. in mm. after 1 hour	Number	%
0—10	67	45
11—20	43	29
21—30	14	
31—40	7	
41—50	6	
51—60	5	
61—70	3	26
71—80	1	
81—90	1	
91—100	2	
101->	1	
Total	150	

*Case 134.*

Girl, 8 years old.

At the age of 6 years the patient was under hospital treatment 3 months for polyarthritis and endocarditis. On admission the sedimentation rate was 138 mm./1 hr. Since her discharge from the hospital, the patient has been free from joint and heart trouble, but for 2 weeks before this admission she has had choreatic jerking of the arms and shoulders. Examination shows a typical picture of chorea, and S.R. is 8 mm./1 hr.

*Case 182.*

Woman, 18 years old.

3 months before admission, the patient was confined to bed at home for 2 weeks with fever, pain and swelling of the foot, elbow, wrist and finger joints after an attack of tonsillar angina. After she got up, the patient has been feeling tired and nervous; and about one month before admission, she had jerking of the shoulders, hands and legs. Examination shows chorea (and cardiac disease). S.R. is 8 mm./1 hr.

Considering these repeated observations of low sedimentation rates in choreic patients with clinically definite rheumatic infection, the only justifiable conclusion about the rheumatic etiology in chorea will be that it seems not to be the same factor in the rheumatic infection that raises the sedimentation rate and produces chorea. With our present knowledge of rheumatic infection, a

discussion of whether or not chorea with regard to the sedimentation rate is to be looked upon as a rheumatic manifestation, or whether the greater importance is to be attached to the sedimentation rate or to the chorea in deciding on the presence of active rheumatic infection can only lead to answers of subjective value.

An account of rheumatic chorea in pregnancy and in mono-symptomatic rheumatic infection will be given later in this chapter.

#### *Conclusion.*

As, in the absence of a diagnostic test for rheumatic infection, a dogmatic definition has to be employed in the classification of the material, the rheumatic chorea material may serve merely to elucidate how the rheumatic etiology of chorea appears clinically under the given conditions. The most common finding in the anamnesis is arthritis (73%); in the hospital it is carditis (68%). The other rheumatic manifestations are seen but very seldom.

Owing to the frequent clinical connection between chorea and rheumatic manifestations as arthritis and carditis, it is only natural that most often chorea too is reckoned as attributable to rheumatic infection. This view may be accepted only with some degree of reservation, as both pathologic-anatomical and bacteriological investigations have been unable to demonstrate any definite etiological connection. The usually low sedimentation rate in chorea (in this material as low as 10 or less in 45% of the cases), suggests that the factor in rheumatic infection which makes the sedimentation rate increase is not the same as elicits chorea.

### **3. Non-rheumatic Chorea.**

Among the 704 first visit attacks of chorea in the present material some cause other than rheumatic infection has been found most likely in 22 cases (3%). These cases have been recorded as non-rheumatic chorea, and this heading covers several different causes of chorea.

These causes of chorea are of minor practical importance in the clinical work because they are encountered but infrequently. They are of great theoretical importance, however, because they

show that clinically the situation is the same in chorea as in arthritis and carditis: the cause is most often rheumatic, but it *may* be something else. Further, in studies of the etiology of chorea, one case which unquestionably is due to some other cause is just as significant as many. Besides, our knowledge of chorea in general has advanced at least as much through studies on chorea of causes other than rheumatic infection as on studies on rheumatic chorea.

### Chorea due to Prenatal Influence.

Among the 704 cases of chorea notified in Malmöhus county in 1910—1944 only 4 persons are entered in the group of chorea due to prenatal influence. This does not mean that cases of birth injury with subsequent appearance of chorea have been limited to this number. The low number merely implies that in these four cases the chorea has been pronounced enough to be included in the diagnosis. They are illustrated fairly well by the following case:

#### *Case 686.*

The patient — a woman, aged 38 — is admitted for examination on account of shaking and twitching of the entire body since the age of 2 years. She is able to walk with support of a cane, but she is unable to take in her food by herself. She can read but not write.

The patient shows continuous irregular jerking of her head, arms and legs, together with athetotic movements of the hands. When she is lying on her back, the head is bent backwards and somewhat to the left, and her legs are crossed, with adduction contracture in both hip joints. Possibly slight muscular hypertonia in the lower extremities. The patellar and Achilles reflexes cannot be estimated on account of the jerking; plantar reflexes uncertain; Babinski's sign present now and then.

An embryonic defect, intrauterine injury (malformation) or birth injury to the brain — injuries of various character and often obscure origin, may involve also the choreatic system. So, among the many symptoms characterizing these morbid conditions, among which Little's disease is the most well-known, chorea may also appear. It is to be mentioned, however, that athetosis or choreo-athetosis is more common — it was also present in the case above.

The greater the chance of birth injury to the brain, the more often we meet with chorea in the diseases due to prenatal influence.

Prematurity is a condition accessible to estimation. Indeed, on follow-up examination of 376 children whose birth weight was 2500 g. or less, Brander (1939) was able at their age of 7—15 years to demonstrate the presence of choreiform movements in 3.5% of these children, and an increasing frequency of this phenomenon with decreasing birth weight.

It is characteristic of this cause of chorea that it asserts itself already in the first years of life — as a rule in the latter half of the first year (Ford, 1946) — and usually together with other signs of injury to the brain: delayed development, mental debility, altered tonus, etc. It takes a chronic, non-progressive course. In the absence of positive data on birth injury, other causes have to be deliberated. Among these, mention is to be made of icteric damage to the basal ganglia in erythroblastosis foetalis. Another possible cause of chorea at this age that has to be considered is encephalitis. Rheumatic chorea is seen but very seldom before the age of three years and never in the first year of life.

In the remaining three cases, we meet with a positive history of forceps delivery in one case, in which the chorea appeared at the age of 2 years. In two cases the prenatal influence as a cause of the chorea is uncertain, as there is no positive history of birth injury. In one of these cases, however, there was imbecility, in the other case delayed mental development, both of which are suggestive of such a factor.

#### *Recapitulation.*

Prenatal influence (embryonic defect, intrauterine injury and birth injury) may be localized so as to involve the choreatic system. Chorea due to such a cause makes its appearance early in life, as a rule in the latter half of the first year, and is often associated with other evidence of injury to the brain. Of the four cases in this group one is mentioned as illustrative.

#### **Chorea due to Hereditary Degeneration.**

In 1872 George Huntington published a paper on chorea in which he reported some observations by himself and by his ancestors on the clinical picture of a chronic progressive hereditary

form of chorea which they had encountered on Long Island and in which the choreic movements constituted the predominant symptom. The disease has since been designated as chronic hereditary chorea or, quite simply, Huntington's chorea. Now Huntington was not the first to describe this morbid condition, as single cases had now and then been reported in the literature previously, but he was the first to emphasize the characteristics of this lesion.

According to Wollenberg (1899) the original work of Huntington is no longer available, but he gave the following criteria of the disease he described:

1. The lesion is hereditary.
2. Its onset is in conspicuous, but it increases in intensity; it often is associated with mental disturbances, and it terminates fatally.
3. The disease never commences in youth, most often at the age of 30—40 years, and it attacks both sexes alike.

To begin with it seemed questionable whether this might be a disease *per se*. But its clinical features, its uniform course and, above all, the pathologic-anatomical findings of degenerative changes, especially in the basal ganglia and cerebral cortex (*e.g.*, Alzheimer, 1911; C. & O. Vogt, 1920; Lewy, 1923) have brought about that in the modern medical literature there is no longer any doubt about hereditary degenerative chorea being a disease in itself. In most of the cases the diagnosis will give no difficulty.

Subsequent observations have shown that Huntington gave all too narrow limits for the age at which chorea first appears. Several cases have been reported in which the disease appeared before the age of 20 years — even in childhood, when rheumatic chorea is most common. Three such cases are mentioned in Nothnagel's handbook (including one patient of 10 years) and Owensby (1925) has reported a case of Huntington's chorea in a 7-year-old girl, whose father, paternal grandfather and two paternal aunts were suffering from the same affection. An interesting observation is the decrease in the age of the patients at the onset that often takes place with each generation (Goldstein, 1913; Kalkhof & Rankee, 1913), through which the years of fertility decrease for each generation. The real cause of this fatal disease is still quite obscure. We are merely able to register the hereditary degenerative factor.

Table 8 gives a schematic survey of the observations on cases of hereditary degenerative chorea in the present material of 704 cases of chorea in the period of 1910—1944. Here we meet with 8 patients who during this period were under observation for this disease. In one family three members were under hospital treatment, in one family two members, and from the remaining families one member of each. Of these 8 patients 7 had died at the conclusion of this investigation. The group includes 4 men and 4 women. The youngest age at the onset is 17 years, the oldest 49, and the average age at the onset is 36—37 years. Two of the patients are under 20 years at the onset. In four of these cases the age at the onset is known also for the preceding generation, in one case for two generations, and in all the present cases the age at the onset is lower than that for the preceding generation, on an average 10—11 years. The duration of illness has been between 5 and 17 years, averaging 9—10 years. The lowest age at death is 26 years, the highest 61, and the average age for the 7 who died is 47—48 years.

A case of hereditary degenerative chorea with onset during pregnancy is reported by Koritkowsky (1904). In our material it is recorded that the trouble commenced in one case in the puerperium; in the case of her mother the disease also commenced during a puerperium.

In one of the families where a mother and her three daughters had hereditary degenerative chorea, a girl in the following generation had an attack of rheumatic infection with chorea at the age of 12 years. The mother of this girl, however, is well.

It will be appropriate here briefly to give an abstract of the case of this girl:

*Case 456.*

Girl, 12 years old, admitted 11/11—9/12 1926.

No previous attack of chorea. Onset about Sept. 3 with painful swelling of both knee joints and both ankle joints, besides pain in the left elbow, shoulder and temporomandibular joints. On admission she showed choreic jerks of the arms, most the right, signs of cardiac changes with sibilant systolic murmur with P. M. in the left I.S. 3, and accentuated P<sub>2</sub>; together with pain on maximal flexion of the right knee joint. At her discharge from the hospital she had recovered from the chorea and the arthritis but showed an organic heart lesion.

This patient is now 33 years old and has not shown any subsequent choreatic symptoms. Whether the familial hereditary degenerative

Table 8. *Cases of hereditary degenerative chorea in Malmöhus county  
1910—1944.*

No	Sex	Age on adm.	Age at onset	First symptom	Course	Heredity	Remarks
687	F	40 years (1912)	38	Jerks of arms and legs. Commenced in puerperium	Died at age of 43 yrs	Mother, two brothers (690), daughter (693)	Mother got ill at age of 42, in puerperium
688	F	19 years (1913)	18	Jerks of arms and legs	Died at age of 26 yrs	Paternal grandfather, father, paternal aunt, uncle, cousin	Father got ill at age of 35 yrs
689	M	50 years (1921)	47	«Nerves disorderly»	Died at age of 60 yrs	Father	
690	M	47 years (1923)	41	Peculiar gait	Died at age of 59 yrs	Mother, brother, sister (687), two cousins (693)	Mother got ill at age of 42, in puerperium
691	M	48 years (1926)	47	Nervousness. Handwriting altered	Died at age of 55 yrs	Father, two sons (692)	
692	M	20 years (1936)	17	Jerks of arms, making stenography difficult	Nursed in home for chronic patients	Father (691), brother	Father got ill at age of 47
693	F	31 years (1938)	27	Jerks of entire body	Died at age of 32 yrs	Mother (687), two maternal uncles (690)	Mother got ill at age of 38, uncle at 41, maternal grandmother at 42 yrs
694	F	59 years (1943)	49	Jerks of arms	Died at age of 61 yrs	Mother, two sisters	Sister's daughter had rheum. chorea at age of 12

chorea has been of any significance to her rheumatic infection manifesting itself in chorea is uncertain.

In this connection it may be mentioned that Kehrer (1928) has tried, though unsuccessfully, to prove that an increased incidence of inflammatory and degenerative chorea occurred in the same family, emphasizing the significance of the constitutional factor in the pathogenesis of chorea.

#### *Recapitulation.*

The cause of the hereditary degenerative chorea, the clinical picture of which was first described by George Huntington, is still obscure. The present material includes 8 cases of heredodegenerative chorea: three members of one family, 2 members of one family and 3 from 3 different families. In this material the youngest age at the onset is 17 years, the average 36—37 years, and the highest age at the onset is 49 years. A schematic survey of this group is given in Table 8. An abstract is given of the case history of a girl of 12 years, with 4 established cases of heredodegenerative chorea in her family history; in her case, however, the chorea was of rheumatic origin.

#### **Chorea due to Infection.**

Chorea as a symptom of damage to the brain from infection other than the rheumatic is considerably less frequent than suggested by the comprehensive literature. Our material of 704 cases of chorea thus includes only 8 cases in which the neurological findings — pleocytosis in the cerebrospinal fluid, nystagmus, and diplopia — are suggestive of inflammatory changes in the brain of a character other than that of rheumatic infection. But in none of these cases could the diagnosis be proved with certainty.

In his large monograph Wicke (1844) mentions »Fieber und entzündliche Krankheiten« among the causes of chorea. From the first comprehensive British investigation into this question, Mackenzie (1887) reported as possible causes of chorea: scarlet fever, measles, whooping cough, varicella, small-pox, mumps, diphtheria, and typhoid fever. And after a thorough study of the chorea literature Gött (1931) exclaims: »... man wird in der Litte-

ratur kaum eine Infektionskrankheit finden können, die nicht beschuldigt wird, einen Veitstanz hervorgerufen zu haben». Thus we should always be very critical in accepting the statements made about infectious chorea of non-rheumatic origin.

No thorough account can be given here of the infectious causes of chorea. Theoretically, however, any infection that may produce encephalitis or encephalopathy is also able to produce chorea. Thus, in keeping with our knowledge of inflammatory diseases of the brain we find chorea described as a symptom in syphilis (e.g., Babonneix, 1923) and tuberculosis of the brain (Schilder, 1911), in acute anterior polioencephalomyelitis (Netter & Ribadeau-Dumas, 1913) and epidemic encephalitis (Stertz, 1921), in measles (Boenheim, 1925) chicken pox (de Toni, 1924), scarlatina (Mackenzie, 1887) and whooping cough (Fanconi & Wissler, 1943). Further, Leichtentritt (1930) has reported that chorea has been observed in several cases together with gonorrhea, and the same applies to influenza.

Among all these infectious causes of chorea, two are of particular interest in this connection: epidemic encephalitis, from a diagnostic point of view, and scarlet fever, from an etiological point of view.

*Epidemic encephalitis*, which after v. Economo's (1917) description also has been designated as lethargic encephalitis, may occur in a hyperkinetic form, too, associated with chorea. Single cases of this lesion were probably known also prior to v. Economo — and one wonders whether an instance of chorea reported as early as 1808 by Gumprecht & Wigand (cited after Wicke, 1844) might not have been due to lethargic encephalitis — as suggested by the following description: » ... fing der vermeintliche Veitstanz bei einem 14 J. M. mit allgemeiner Lebhaftigkeit des rechten Arms an und ging in unaufhörliches Dehnen, Heben und Schlenkern der Arme und Beine, Drehen, Werfen und Schaukeln des Kopfs, Verzerrungen des Gesichts und in eine undeutliche, zitternde und hüpfende Sprache über, es folgte Schlafsucht und Opistotonus und an 9 T. der Tod».

As epidemic disease, lethargic encephalitis was observed first in Vienna in January 1917, and then it overran most of Europe in 1918—19, reaching Canada and U.S.A. in 1919 (Scheinker, 1947). During and after this wave of encephalitis, in several parts of the world it was found that some of the cases which had been diagnosed as «chorea minor» were due to lethargic encephalitis. In other words,

the clinical picture of rheumatic chorea and that of cases due to epidemic encephalitis may be identical. It will be appropriate here to cite a few of the cases reported at that time:

Harvier & Levaditi (1920) describe a case that terminated fatally and in which chorea and fever were the only symptoms observed. On autopsy the authors were able to show that the brain presented a picture suggestive of epidemic encephalitis. They inoculated a rabbit with brain tissue and the animal subsequently showed clinically choreiform movements of the extremities, and pathologic-anatomically a picture as seen in encephalitis.

Sicard (1921) describes the case of a pregnant woman with chorea without any of the classical signs of lethargic encephalitis (eye trouble, somnolence, clonic jerks) and in which the cause of the chorea was not revealed till later on when Parkinson's syndrome made its appearance.

Lesné & Baruk (1924) report their observations on a child who in June 1919, at the age of 14, presented «l'apparition d'une chorée qui présentait le tableau classique de la chorée de Sydenham». The patient who had fever showed never any rhythmic movements, myoclonus, disturbances of sleep or eye symptoms. In Sept. 1919 the patient left the hospital feeling perfectly well, but in July 1922 she had tremor, reduced motility and rigidity.

The experiences from these and similar cases are summed up by Collis (1937), saying: »It seems clear then that the virus of epidemic encephalitis, and possibly other similar viruses, will produce a condition which may be clinically indistinguishable from Sydenham's chorea». The contribution of epidemic encephalitis to the chorea diagnostics implies that a morbid condition with chorea, or chorea and fever, should not be taken to be of rheumatic etiology. The non-epidemic but sporadic occurrence of encephalitis nowadays certainly makes it necessary in every instance of chorea with uncertain etiology to consider the possibility of encephalitis.

The possibility of encephalitis as a cause of chorea in pregnancy will be dealt with in a subsequent section.

*Scarlet fever* is the infectious disease which, next to rheumatic infection, is mentioned as the most common cause of chorea. Etiologically this observation is of interest because we know that scarlet fever is produced by streptococci, and that there is a clinically as well as bacteriologically verified connection between rheumatic infection and streptococci.

The connection between chorea and scarlet fever was mentioned already by Broadbent in the great discussion about the cause of chorea in the Royal Medical and Chirurgical Society in London on

May 26, 1885. In his collation of 439 cases of chorea, Mackenzie (1887) found rheumatism in 40% and scarlet fever in 29%. Subsequent investigations show considerably lower figures. Thus, Wollenberg (1899) found a preceding attack of scarlet fever in the history of the patient in 3 out of 113 cases. Jolly (1900) takes scarlet fever as a cause of chorea to be rare; Nordgren (1923) finds scarlet fever in the history of the patient in 6 out of 343 cases with chorea; Wallace (1933) in 6 out of 215 cases, and Gerstley *et al.* (1935) in 4 out of 44 cases.

A study of the present material with regard to notes about scarlet fever in connection with chorea shows that a chronological connection is recorded in 18 out of 682 cases of chorea of rheumatic or obscure origin. This figure is to be looked upon as a minimum, because the material was not arranged for this purpose from the start. For the 467 cases of rheumatic chorea connection is recorded in 16 cases; the remaining 2 cases are found among the 215 cases of cryptogenetic chorea. In 12 cases the appearance of scarlet fever is recorded as prior to that of chorea, in 6 cases during the treatment for chorea. In the 12 cases the connection with the chorea was looked upon as established by way of a suppurating scarlatinal otitis, and the longest duration of the otitis was 3 years, the shortest 4 months. In 6 of the remaining 8 cases the interval between the discontinuance of epidemiological regimen and the appearance of chorea varied from 3 months to «immediately after»; and only in 2 cases is it recorded that the chorea was noticed at once when the patient returned home from the epidemic hospital; in no case is there any note about the patient being transferred from the epidemic hospital to another hospital for treatment of the chorea.

With our present knowledge it is not practicable to decide whether this time relation which through the years now and then has been observed between scarlet fever and chorea also is a causal connection. The relation between chorea and rheumatic infection and scarlatina, and between these three and the streptococci, has not yet been fully elucidated, and thus the foundation is wanting for a discussion of the etiological significance of scarlet fever to chorea.

The same question viewed under an epidemiological angle will be discussed in Chapter V.

### *Recapitulation.*

Infection other than rheumatic may also cause chorea. Thus the occurrence of chorea has been described in syphilis, tuberculosis, acute anterior poliomyelitis, epidemic encephalitis, measles, chickenpox, whooping cough, gonorrhea and influenza. Among these, epidemic encephalitis and scarlet fever are of greatest interest. Epidemic encephalitis may give a clinical picture identical with that of monosymptomatic rheumatic infection. Scarlet fever attracts particular interest because, according to the literature, next to rheumatic infection it is the most common cause of chorea.

The present material includes 8 cases of suspect encephalitis as the cause of chorea. Connection with scarlet fever is recorded in 18 out of 682 cases, but whether there also be an etiologic connection in these cases cannot be decided.

### **Chorea due to Intoxication.**

Chorea from exogenous or endogenous intoxication is a rare phenomenon, and in the present material no instance may be ascribed with certainty to such a condition. In the literature, however, a few instances of chorea have been reported that were due to intoxication.

The increased affinity of *carbon monoxide* for the basal ganglia, illustrated in particular by its effect on the globus pallidus, shows that in this form of intoxication it is reasonable especially to expect chorea to turn up as a symptom. Bäumler (1933) has also described a case of illuminating gas poisoning in a girl, 11 years old, which on the 6th day presented a typical chorea: the girl was moving constantly, while she was unable to stand or walk, and there was pronounced muscular hypotonia. Gradually the symptoms subsided completely.

In carbon monoxide intoxication, however, chorea is no common symptom. Zahle (1948), who has given a comprehensive survey of the symptoms in acute carbon monoxide intoxication, describes only four cases of extrapyramidal hyperkinetic manifestations: chorea in three, athetosis in one.

The *toxin* which is formed by Löffler's *diphtheria bacillus* and which post-diphtherically attacks in particular the peripheral

motor neurones (paralysis of the soft palate, paralysis of accommodation, generalized polyneuritis) may in somewhat rare cases attack the central nervous system and in this way give rise to chorea. The first observation of this kind was described by Globus (1923) in the case of a woman, 29 years old, who died with the features of epidemic encephalitis with chorea, and who on autopsy was found to have been suffering from diphtheric colpitis, with positive diphtheric findings in the cerebrospinal fluid and severe parenchymatous damage of non-inflammatory character localized exclusively to the corpus striatum. Another case, more significative, is described by Critchley (1924):

A girl, 14 years old, with faecal diphtheria, is discharged, apparently well, from the hospital after 37 days. Four weeks later she has signs of paralysis of the soft palate and accommodation, and one week later also symptoms of polyneuritis of the left extremities. At the same time there are lively movements of the entire right side of the body, besides grimacing. This condition is aggravated when she gets tired. There is no evidence of rheumatic infection, no abnormality of the heart. Four months later this trouble has subsided completely.

Two cases of post-diphtheric chorea are also described by Huber (1937), but he thinks that a rheumatic infection is more likely as the cause of the chorea in one of the cases.

Diphtheria toxin has also been employed in the experimental chorea research (e.g., Lewy, 1922). Lewy injected diphtheria bacilli subcutaneously into white mice and obtained choreiform movements of the animals, which on autopsy showed changes of the small cells in the neostriatum.

Our material, especially from the earlier years, includes some cases of approximate clinical coincidence of chorea and diphtheria, but in no instance was there any particular reason to suspect a causal connection. As a rule, these patients had their attack of diphtheria after treatment for chorea had been instituted.

*Endogenous intoxication* as a cause of chorea plays a great rôle in the discussion of the causes of chorea in pregnancy. However, the significance of toxemia of pregnancy to the appearance of chorea is obscure, for which reason an account of this cause will be given in the section on cryptogenetic chorea.

### Chorea due to Circulatory Disturbance.

Chorea may be brought about by impairment of the blood supply of the choreatic system. The basal ganglia in the midbrain are supplied by the middle cerebral artery which, before reaching the Sylvian fissure, gives off a series of small branches passing more or less vertically upwards to the basal ganglia (Scheinker, 1947). The middle cerebral artery lies in the direction of the current from the carotid artery and heart, which implies that the region supplied by this artery is a site of choice for embolism.

The knowledge about the frequent occurrence of heart changes in chorea once gave rise to the embolic theory (Kirkes, 1863) to explain chorea as attributable to «the presence of cerebral capillary plugging». Towards the end of the nineteenth century, however, it was realized that arterial embolism unquestionably might sometimes be the cause of chorea but not as a rule (Broadbent, 1869; Duckworth, 1885). Arterial embolism as a cause of chorea, it was pointed out, has to be put down as a rare phenomenon, and in this material it occurs but once:

#### *Case 703.*

Woman, 36 years old. Diagnosis: Incompensated heart lesion (mitral stenosis) + cerebral embolism + hemiplegia, left + chorea, right + pulmonary infarction.

At the age of 11 years the patient had rheumatic fever with chorea and heart lesion, and since then she has readily become out of breath. Four hours before admission to the hospital her left arm and leg became limp, and she had twitchings in the right arm and leg so that she had to be carried to bed. The mouth deviated to the right.

On admission the patient is very anxious and poorly. There is facial paralysis on the left side. The patient is unable to move the left arm, but she can move the left leg. Chorea jerking is felt in the right arm and leg. Babinski's sign on the left side. Auscultation of the heart shows arrhythmia, together with a presystolic blowing murmur over the apex and accentuated first sound.

After 34 days the patient was able to get up, and a week later she was discharged, to her home, with the following final remark: no choreic twitching; some impairment of the muscular power of the left arm and leg, together with moderate ataxia on the same side.

Other vascular causes of chorea besides embolism are thrombosis and hemorrhage. It is characteristic of all these causes that they most often appear suddenly, and that as a rule they give rise to hemichorea

and are accompanied by other signs of damage to the brain. They are of greater theoretical than practical interest as no active therapy is yet available. Thus, Martin (1928) was able to show that a common pathologic-anatomical finding in these cases of hemichorea is enlargement of the body of Luys, and he thinks that as long as this structure is intact chorea seems not to occur in focal injuries. Krabbe (1947) mentions the same localization and assumes that this is the site of the lesion also in «chorea minor».

When hemiplegia and chorea occur in the same patient, the chorea sometimes is preceded by the hemiplegia, up to a few months (post-hemiplegic hemichorea). It happens but very seldom that the choreic motions appear prior to the hemiplegia (prehemiplegic hemichorea), signifying defective blood supply to nerve cells (Bing, 1945).

Our material includes one case (No. 704) which most likely represents the vascular etiology of chorea.

This patient was a woman, 72 years old, who for 8 years prior to her hospitalization had been treated for arteriosclerosis and now, in the last two months, was troubled with a steadily increasing restlessness of the left arm and leg, besides the head. She has fallen twice in attacks of dizziness. Nothing positive is known about hereditary disposition to any organic nerve lesion. At the examination the patient is unable to lie quiet, having continuously large, jerky and rapid movements in the left arm and leg, also in the head. There is hypotonia of the left arm and leg, but no definite ataxia. The patellar reflexes are lively, but equal, and the plantar reflexes cannot be elicited. At her discharge from the hospital she had improved somewhat. She returned two years later with the same features of motility and the same neurologic picture.

This case calls attention to the very rare cases of arteriosclerotic chorea (Stertz, 1921; Lewy, 1923), which largely show the same features as Huntington's chorea, except that here the hereditary factor is absent. The clinical diagnosis of this cause, however, will always imply some degree of uncertainty.

In the clinical picture of the morbid condition in which vascular chorea plays a part the chorea is usually not the dominating symptom, the other deficiency symptoms attracting more interest. So it is reasonable to assume that even though this form of chorea is rare it is observed at the examination of the patients more often than recorded under the symptomatic diagnosis.

### Chorea due to Disorder of the Metabolism.

No definite case of chorea due to disturbance of the metabolism is found in this material. Still, such a cause of chorea has been reported in the literature so often that it is only reasonable to mention it here, too.

Because chorea most often occurs in the years immediately before puberty, the question about an *endocrine factor* in chorea has been raised. Also the increase in the incidence of chorea during pregnancy is suggestive of an endocrine factor. But even though these things were realized long ago we still know but little about them. In particular the relation between hormonal activity and rheumatic infection requires further elucidation.

Parathyroid dysfunction has been suggested as a possible cause of chorea. Thus Morini (1921) calls attention to hypofunction of the parathyroid, and Kehrer (1942) points out that chorea has the same tendency to relapse as tetany. Warner (1930) found in chorea a decrease of 15% in the calcium content of the cerebrospinal fluid — which would be enough to explain the increased irritability of the cerebral cortex. His result has not been confirmed.

Thyroid hyperfunction as a cause of chorea has been discussed especially by Kundratitz (1927) who raised the question whether «ein Teil der Symptome bei dem voll ausgebildeten Krankheitsbilde der Chorea auf thyreotoxischen Einfluss zurückzuführen ist». He calls attention to the many points of resemblance in the clinical pictures of chorea and thyrotoxicosis — from the hereditary constitutional factors and frequent association with psychic trauma to vasolability, muscular restlessness, etc. However, he found enlargement of the thyroid but seldom, and he made no determination of the basal metabolism. Warner (1930) and McCulloch (1938) were able to report that whenever it had been possible to determine the basal metabolism in cases of chorea, they had found the rate to be normal. Poynton (1927) is also interested in the relation between chorea and thyroid function, and he mentions a girl of 13 years who had two attacks of chorea and coincident hyperthyroidism. Poynton also mentions the case of a girl, 16 years old, with rheumatic chorea and enlargement of the thyroid together with tremor, all of which subsided on treatment with Lugol's solution. In conclusion he emphasizes that the relation thyroid —

chorea is of considerable interest but then he says: »In some cases I have noticed enlargement of the thyroid, but in hundreds I have seen no change.«

In Sweden, Faxén (1933) reported a material of 117 children with chorea, among whom he found 2 with exophthalmus, in one of whom the rate of basal metabolism was increased.

In more recent years the relation between chorea and the thyroid has again become somewhat topical after Coburn (1945) pointed out that hyperthyroidism and rheumatic fever have some factor in common, saying: »The collected observations indicate that there is probably a constitutional defect common to these two disease processes and that perhaps hyperthyroidism increases rheumatic susceptibility.«

The resemblance of the clinical features in rheumatic infection with chorea to those of hyperthyroidism may give diagnostic difficulties that are illustrated very well by the following case:

*Case 193.*

Woman, aged 17. Adm.  $\frac{4}{6}$ — $\frac{6}{7}$  1934.

Past history negative except for measles in childhood. In the last 5 years the patient has often caught cold, with sore throat and high fever for 2–3 weeks. The last attack of this kind was in Feb.—March this year. Never any joint complaints.

In January 1933 the factory physician ascertained that the patient had a goiter, which she does not think now has become larger. She has always felt nervous, but in the last couple of months she has been troubled with twitchings in the arms and legs, she has been restless and has had headache. She has become tired and has lost 6 kg. in weight within the last 6 months. There has been no palpitation or breathlessness.

Clinical status on  $\frac{4}{6}$  1934: The patient does not lie quiet in bed, plucking at the bedclothes. Now and then choreatic jerks in the arms and legs. The gait is somewhat jerky. Finger-nose and knee-heel tests show no abnormality. Muscular tonus somewhat lowered. No exophthalmus. No tremor of the fingers or tongue. No tachycardia. The thyroid shows moderate diffuse enlargement. Auscultation of the heart: Borders normal; sounds clear; rhythm regular. Blood pressure: 110/65 mm.

Sedimentation rate: 2/6 mm. Rate of basal metabolism: +3 and -6%.

The question has been raised by Schleicher (1939) whether chorea perhaps may be a symptom of *vitamin B* deficiency, as it improves on treatment with thiamine and yeast. Schwartzman *et. al.* (1941) subscribed to this view, as they obtained good results from treatment with vitamin B6 (synonyms: pyridoxine, adermin).

The puzzling chorea occurring in the senium in cases offering no evidence in support of Huntington's chorea or vascular chorea, may perhaps be due to a disturbance of the metabolism, with physico-chemical changes in the brain substance »im Sinne des Alterns» (Kihn, 1933).

Most papers on chorea due to disorder of the metabolism are expressions of speculations rather than of facts. Our knowledge concerning the etiology of chorea is so defective, however, that even loosely founded speculations are to be taken into consideration.

#### *Recapitulation.*

In the literature a disorder of the metabolism — as a rule an endocrine disturbance, above all, parathyroid and thyroid — has been discussed as a cause of chorea. Also vitamin deficiency has been suggested as a cause. No definite case of chorea due to disturbance of the metabolism is found in the present material. A case of rheumatic chorea is mentioned, in which the clinical picture showed some points of resemblance to hyperthyroidism.

#### **Chorea due to Neoplasms.**

Chorea due to neoplasms will be mentioned here only because this etiology of chorea may occur. No case of chorea with this etiology is found in the present material, however, and only few cases have been reported in the literature.

Bonhoeffer (1897) has described the case of a woman, 55 years old, with chorea chiefly in the right arm and leg, who died of an intercurrent attack of erysipelas. On autopsy and following microscopic examination Bonhoeffer found a tumor, undoubtedly a metastasis of cancer, at the crossing of the cerebral peduncles, rather more on the right side. He gave an extraordinarily thorough and careful description of the case. Indeed, his observations have been of importance to our conception of the cerebral localization of chorea.

In his survey of the extrapyramidal diseases in childhood, Ibrahim (1930) mentions that tumors in the basal ganglia of the brain have been observed several times. Still, he gives no description of such cases associated with chorea, only of cases with other extrapyramidal symptoms.

Still (1918) describes a child about ten years of age in which a cerebral tumor gives rise to chorea, which, according to Collis (1937), may be »mislabeled as Sydenham's chorea«. Collis thinks that such a situation must be a medical curiosity. The possibility of a cerebral tumor as a cause of chorea is certainly only of slight practical importance. In principle, however, it means that in chorea of obscure etiology we have to reckon also with this possibility.

#### 4. Cryptogenetic Chorea.

In the present material the forms of chorea which do not meet the criteria adopted for rheumatic chorea or fail to give evidence of any other demonstrable cause are entered under the heading of cryptogenetic chorea. This group of chorea comprises 215 cases. In some degree the size of this group indicates a deficit in positive data concerning the individual cases, but it also signifies that even in a good many cases where the thoroughness of the examination and the length of the observation period otherwise seem sufficient there will not infrequently be no definite evidence of the cause. This group gives rise to discussion of some elusive causes that have played a considerable rôle in the development of our knowledge of chorea and which we cannot yet leave out of consideration altogether. Here we shall deal merely with four potential causes or contributory factors of this category, namely, individual constitution, psychic pressure or trauma, pregnancy, and monosymptomatic rheumatic infection.

#### Chorea as a Constitutional Feature.

Chorea as expression of a neuropathic constitution is a conception that was particularly topical in the days when chorea was looked upon as a functional disturbance, not as evidence of injury to the brain. This conception has prevailed a long time, in particular, as an explanation of why rheumatic infection gives rise to chorea in some cases, not in others. From the earlier days of the recognition of the rheumatic infection we thus meet with the following view asserted by Thomas (1885): »Das unbekannte Virus des Polyarthritis acuta kann nun bei einer gewissen Konstitution und gewissen äusseren Bedingungen wirksam sein.« Further, we meet with the neuropathic

constitution as an explanation of chorea in cases presenting no evidence of an exogenous cause. Thus Kirkes (1863) thought that the subjects of chorea are commonly those who possess in a marked degree what is called a nervous temperament». More recently Guttman (1927) speaks of »eine konstitutionelle Erkrankungsbereitschaft der choreatischen Systeme».

The view that the appearance of chorea depends on the presence of one or more constitutional factors is expressed in two elaborate theories: the conception of chorea as a developmental disease, and the theory of choreatic equivalents.

Sydenham (1686) was quite aware that the disturbance of the motility he described occurred most often in the growing years. Not only was this observation confirmed by subsequent investigators, but in the beginning of the 19th century it also was assigned etiological importance when *the very development* of the individual was considered the cause of chorea. Thus Wicke (1844) refers to Wilhelm (1825) the view that during puberty the developmental rate of the muscular system proceeds more rapidly than that of the nervous system and that this gives rise to peculiar state of irritation manifesting itself in the form of chorea. Joffroy (1885), Comby (1888) and others held that chorea may appear spontaneously under the influence of a neuropathic habitus and the age. This asserts itself especially in girls, as the development during puberty is of greater significance in »the more excitable female sex than in the male».

As to the question about developmental chorea in the present material, the age curve for the first onset of chorea (Fig. 6, p. 105) may offer some contribution. It shows that the typical age for the first onset of chorea in the entire material is 8—11 and that it begins to fall rather abruptly even at the age of 12 years, that is, at the time when the development of the individual still is in full swing. Considering the sex, we find that the typical age for the onset of chorea in boys is as early as 8 years, for girls not until 11 years. In view of the fact that puberty comes earlier in girls than in boys it had been expected that the onset of chorea would appear earlier in girls than in boys. It seems reasonable, therefore, from the present findings to hold that the frequency curve for the age of the patients at the first onset of chorea in some degree certainly coincides with the age of the individual for development and growth, but the form

of the curve is not identical. And taking the sex into account too, the discrepancy becomes so great that we may hardly be inclined to ascribe any etiological significance to the development in itself.

The theory of *choreatic equivalents* is based on the view that a general inferiority of the nervous system is a prerequisite of the manifestation of chorea, and that this disposition to chorea may be realized also in other nervous disturbances. Wollenberg (1899) found psychopathic and neuropathic strain in 36.6% of 112 choreic patients, and Runge (1910), who thoroughly worked up a total of 116 cases of chorea, found nervousness and nervous diseases to be considerably more common among the parents and sibs of choreic patients than among normal persons. In Sweden this view attracted particular interest through the follow-up examination reported by Forssner (1910) of 28 cases of chorea among children from which he found »dass Chorea vorwiegend schwache auch in anderen Beziehungen wenig widerstandskräftige Konstitutionen befällt». Guttman (1927) formed the term »eine konstitutionelle Erkrankungsbereitschaft der choreatischen Systeme» after a study of 18 families with chorea, among which he found attacks of hysteria, epilepsy and other disturbances of mobility in 15.

The theory about a choreatic equivalent was systematized chiefly by Kehrer (1928) who pointed out the increased frequency in choreic families, in the first place, of migraine, epileptiform attacks, adiposis and nervousness, in the second place of early attacks of hemiplegia, oligophrenia, etc. The same idea could be noticed even earlier in the French literature when, for instance, chorea was mentioned as associated with »l'hérédité de transformations» (Leroux, 1905). This idea has by no means remained uncontested, but here it will suffice to mention that Sutton & Dodge (1938) have reported a very thorough examination of 100 choreic children, among other things, with determination of their intelligence quotient, in which they found I.Q. to be normal, and they were unable to corroborate the statement that children with chorea »have any particular personality or body type».

*Heredity* is a constitutional etiological factor which in chorea has excited a good deal of interest. The special hereditary aspects of Huntington's chorea have been mentioned already. On correlation of several choreic materials, Wollenberg (1899) found 2% chorea among the parents, 5.3% among the sibs.

In spite of the uncertainty with which the collection of the present material was encumbered, it still may contribute something of interest to our understanding of the significance of heredity to the occurrence of chorea.

In the compleutive follow-up examination of the present material — in which the choreic patients answered the question whether chorea had occurred among their parents and sibs — 425 of the patients in the group of rheumatic chorea and in the group of cryptogenetic chorea have given serviceable answers. Among these 425 cases chorea had occurred in the father in 1 case, in the mother in 10 cases, and among the sibs in 21 cases (708 brothers with 6 cases, and 693 sisters with 15 cases of chorea).

On calculation of the percental incidence of chorea among the population in Malmöhus county 1910—1944, the probability of the individual persons to become ill with chorea is found to be 1.5%<sup>1</sup> for the males, 3.2%<sup>1</sup> for the females.<sup>1</sup> So, when in the present material it is ascertained that among 425 cases of chorea, chorea among the respective fathers was ascertained in one case, this is about what was expected. In contrast hereto, a considerable overrepresentation of chorea among the relatives is indicated by the circumstances that among the mothers of the 425 patients chorea was ascertained in 10 as against the expected 1—2 cases, that this material shows 6 cases of chorea among 708 brothers of our patients as against the expected 1 brother, besides 15 cases of chorea among 693 sisters as against the expected 2 sisters. Reckoned in percentages, then, 2.6% of the parents and 1.5% of the sibs are found to have had chorea.

So, these figures show that unquestionably we have to reckon with a constitutional hereditary factor in the etiology of chorea. In our days, however, the interest — quite correctly — is not attached exclusively to the hereditary aspect of chorea but also to the heredity of rheumatic infection. Thus the question about the inheritance of chorea becomes merely a detail in a more comprehensive investigation, the performance of which requires strict diagnostic criteria during a considerable length of time and most critically. Here it will be appropriate to refer the reader to the modern review of these aspects given by May Wilson in the American Journal of Medicine 2, 190, 1947.

*Conclusion:* The constitutional habitus of the individual has been advanced as an explanation of why rheumatic infection does not give rise to chorea in every case and also why chorea may occur

<sup>1</sup> The procedure in the calculation of this risk is the same as employed by Gustaf Petrén in »Om den årliga frekvensen akuta appendicitfall i Malmö, Lund, Hälsingborg och Uppsala». Svenska Läkartidningen 30:1529, 1941.

in the absence of any demonstrable cause. This idea has afforded the basis for the view of chorea as a developmental disease and also for the theory of choreatic equivalents.

Concerning the difficult question about the significance of the constitution to the occurrence of chorea, the present material may offer the following contribution:

In this material the typical age for the onset of chorea is lower for boys than for girls. If the physical development in itself were the cause of chorea, the girls with their earlier puberty ought to have their onset of chorea earlier than the boys. From the present material it is evident that heredity is a constitutional factor of significance to the occurrence of chorea. There is a marked over-representation of chorea among the parents of our patients as well as among their sibs. From the compleative follow-up examination it is evident that 2.6% of the parents and 1.5% of the sibs of our patients have had chorea.

#### Chorea due to Psychic Pressure or Trauma.

Emotional disturbances such as fright, accident and worry about school are often mentioned as causes of chorea — not only in the older literature where chorea was looked upon as a form of neurosis. Sturges (1881) found »mental or psychic causes of chorea» in about half of his cases, and even 50 years later Gerstley *et al.*, (1935) in their studies on 150 patients over 7 years, with social investigation into 58 of the cases, arrived at the conclusion that »... in our series psychic trauma resulting from fright or overwhelming grief stood out far more strikingly than did any history of infection». Usher (1938) is »... inclined to think that the psychic element plays a much greater rôle than has been attributed to it». In a work dealing chiefly with the often normal sedimentation rate in chorea and with the question whether or not chorea be a sign of rheumatic activity, also Coburn & Moore (1937) leave the door open for psychic trauma as a cause of chorea.

Poynton (1920) found this question so important that he has made it the object of an investigation out of the ordinary in its planning. He reckons that the air raids on London in the first world war ought to have caused so many fright reactions that, if fright were a cause of chorea, the incidence of chorea during the war ought to have been higher than before as well as after the war.

He found no such increase, however. He summarizes the appraisal of his findings as follows: »... and in our opinion the vast experiment of the air raids conclusively proved that fright, although a factor, is not the cause of chorea».

Wall (1920) obtained a history of fright in 66 out of 268 cases of chorea. He thinks, however, that all children are frightened some time or other, and, as fright undeniably increases the choreatic movements, it naturally may sometimes be taken as a cause, even from no adequate reason. As to the relation between chorea and the school, he thinks: »It is not good for a choreic child to attend school, but it is very difficult to get evidence that schooling is really responsible for making a healthy child choreic».

This question has also been the object of a comprehensive investigation reported by Sutton & Dodge (1938) who among 411 attacks of chorea found a connection between its onset and fright, accident, worry about school, and so forth preceding within two months the onset for 21 (9.6%) of the 217 first attacks, and for 18 (9.2%) of the 194 subsequent attacks. In conclusion, however, these authors state: »The fact that the etiology of a clinical syndrome is obscure is to us not justification to ascribe its origin to such a nebulous state as »psychic trauma» ...».

Still, the clinical fact remains — which is substantiated by everybody who has met with a fairly large number of choreic patients — that the patient himself not infrequently gives an emotional factor as the cause of his chorea. This applies also to the present material. In the compleutive follow-up examination the patients were requested to answer this question: What do you reckon yourself as the cause of your attack? Of the patients with rheumatic chorea 245 answered this question, and 59 of them gave some emotional factor or overexertion as the cause. The answers varied from »frightened by a cat» or »nearly run over» to »riding on a scenic railway (hill and slope)», from »harsh upbringing» or »psychic maltreatments» to »my father was often drunk», and from »hard work and harsh treatment» or »overexertion in school» to »over-exertion as seamstress». The cause most often given by the patients is overexertion or troublesome family life.

From the experiences reported in the literature and the present material it might not be quite justifiable to exclude that the psychic factor may be of significance to the appearance of chorea. From daily experience we know that the emotional factor may have some influence on the motor aspects of the individual: that joy and sorrow, tranquility and fear may be reflected by the motions of the individual. To the psychiatrist chorea is familiar as an expression

of an hysterical reaction, and every clinician knows that the choreatic motility is accentuated when the patient feels himself under observation. Indeed, the definition of chorea implies that the motility is accentuated by affect.

With regard to this point, then, we have to recognize that »psychic trauma« may play a rôle in the development of chorea. But this does not necessarily mean that the psychic change is an etiological factor. More likely its significance is limited to the pathogenesis: that the emotional factor may contribute more or less to the manifestation of chorea, regardless of the cause. As early as towards the end of the past century, Marfan (1897) stated that in the cases where a strong emotional affection is given as the cause of chorea it will be more correct to imagine that the emotional affection simply is aggravated by a previously unnoticed chorea.

Here we find ourselves in the border zone between the psychic and the mental domain that is most difficult to estimate, and we have to agree with Cobb (1921) when he says that »the whole subject is an obscure but interesting one».

*Conclusion:* In the literature — the old as well as the more recent — emotional disturbance or overexertion is often recorded as the cause of chorea. In the present material, for instance, 58 out of 245 patients have given an emotional factor or overexertion as the cause of their chorea. In my opinion a psychic factor will not infrequently play some rôle in the development of chorea, being of some significance to the pathogenesis of the lesion, not to the etiology.

#### **Chorea in Pregnancy.**

It is a very old clinical observation that chorea sometimes coincides with pregnancy. The first coincidence of this kind reported in the literature was published by Horstius in 1661 — as quoted by Willson and Preece (1932), who presented a collation of all the cases of chorea and pregnancy reported in the literature up to September 30, 1930. To this list they have added 105 choreic pregnancies, of which they observed 1 case themselves, while members of the various American Obstetrical Societies observed the other cases, and thus the authors were able to report the findings in 797 women with 951 pregnancies. A less comprehensive survey of

chorea in pregnancy has been given by Kehrer (1942) in »Der Veitstanz der Schwangeren (sogenannte Graviditätschorea)«. Judging from these figures, the coincidence of chorea and pregnancy appears to be a rather rare morbid condition. Willson & Preece (1932) found the frequency of pregnancy associated with chorea in the obstetric clinics to be 1:2252 pregnancies, and they emphasize that many obstetricians never have occasion to see any such case.

The present material of 704 cases of first visit chorea includes 477 women, among whom the coincidence of chorea and pregnancy is recorded in 18 cases (3.8%). A survey of these 18 cases is given in Table 9. The youngest of the patients was 19 years, the oldest 34.

Etiologically the appearance of chorea in pregnancy is of great interest, as, besides pregnancy, nearly all the causes known to be able to produce chorea have to be taken into consideration here. In the earlier literature, a great deal of etiological significance was attached above all to the fear implied by undesired pregnancy. This idea has been well expressed by Ruhemann (1889), who says: »In der Regel sind die an Chorea leidenden Schwangeren Erstgebärende und zwar meist sehr jugendlichen Alters, für welche der ihnen ungewohnte Zustand, die Angst vor den Schmerzen der vielleicht noch fernen, aber sie sicher erleidenden Geburtsstunde eine Quelle immerwährender Aufregung ist. Dazu kommt, dass die Betroffenen, wie man beobachtet hat, oft ausserehelich geschwängerte Personen sind, welche naturgemäß von noch weit grösseren psychischen Qualen heimgesucht werden.»

In the modern literature, as represented in particular by Willson & Preece (1932) and Kehrer (1942), however, the discussion of the etiology is conducted chiefly along the following lines:

- I. Is chorea in pregnancy identical with chorea in childhood, probably a rheumatic chorea, in this way:
  - a) really accidental coincidence, or
  - b) relapse during pregnancy of a previous chorea?
- II. Is chorea in pregnancy a toxemia of pregnancy?
- III. Are choreic manifestations in pregnancy due to epidemic encephalitis?

The possibility of a mere *accidental coincidence* of chorea and pregnancy is gainsaid by several facts. Mackenzie (1887) has reported that in a material of 439 choreic patients of all ages only 4—5% be-

Table 9. Schematic survey of 18 cases of chorea during pregnancy among 704 first visit cases of chorea in Malmöhus county in 1910-1944.

Case No.	Hospital	Year	Age	Parity	Month at onset of chorea	Fate of pregnancy	Previous chorea	Previous rheumatic infection	R o m a r k s
139	Med. Clinic, Lund	1912	33	V	Onset prior to pregnancy	Spontaneous delivery of twins	1' attack 8 years ago	Valvular deformity through the last 3 years	Chorea commenced during 2 <sup>o</sup> pregnancy, 8 years ago; never all gone, but worse during each pregnancy. Died of cardiac insufficiency 15 days after delivery
140	Med. Clinic, Lund	1912	21	I	4' month	Spontaneous delivery	No	Joint complaints and swelling 1 year ago	
203	Gyn. Clinic, Lund	1910	26	I	6' month	Spontaneous delivery	At the age of 8 years	Arthritis 4 years ago	Well since. No more children
204	Gyn. Clinic, Lund	1911	30	I	8' month	Spontaneous delivery	At 15 and 20 years	—	Died 1927 of heart disease
205	Psych. Clinic, Lund	1931	23	I	7' month	Spontaneous delivery	No	No	In 8 <sup>o</sup> month hallucinations. Improved before and well after pregnancy. Five subsequent pregnancies without abnormalities. Adm. to Med. Clin., Lund, 1936/1-1937/8 for rheumatic fever

[Triglycerides] [Total cholesterol] [Urea] [Creatinine] [Sedimentation rate]

[Albumin] [Globulin] [Urine] [Urobilinogen]

289	Med. Clinic, Malmö	1919	20	I	7' month	Spontaneous delivery	At the age of 10 years	First time at the age of 5 years. Valvular deformity present	Urine: no albumin.
299	Med. Clinic, Malmö	1931	23	I	7' month	Caesarean section in 7' month	No	Arthritis in child- hood. Valvular deformity present	Died of septicemia 2 weeks after Caesarean section
496	Gyn. Clinic, Lund	1911	19	I	5' month	Spontaneous delivery	No	No	Chorea gone in 6' month. 4 subsequent pregnan- cies without abnorma- lities
497	Gyn. Clinic, Lund	1912	19	II	2' month	—	No	No	Chorea gone in 3' month
498	Gyn. Clinic, Lund	1912	20	I	3' month	Spontaneous delivery	No	No	Chorea gone post partum. Well since. No more children
522	Med. Clinic, Malmö	1910	26	I	—	—	At the age of 18 years	No	Relapse in 2' pregnancy
562	Med. Clinic, Malmö	1916	34	V	1' month	Spontaneous delivery	No	No	No subsequent preg- nancies. Eldest child has had chorea
567	Med. Clinic, Malmö	1924	22	II	3' month	Vaginal hys- terotomy, anterior+ evacuation+ of uterus in 3' month	No	No	Improved after opera- tion. Diplopia and nys- tagmus

Table 9 (cont.)

Case No.	Hospital	Year	Age	Parity	Month at onset of chorea	Fate of pregnancy	Previous chorea	Previous rheumatic infection	Remarks
569	Med. Clinic, Malmö	1925	19	I	1' month	Spontaneous delivery	No	No	One subsequent pregnancy without abnormalities
584	Gyn. Clinic, Malmö	1923	22	I	—	Spontaneous delivery	—	—	Chorea improved after pregnancy
585	Gyn. Clinic, Malmö	1931	19	II	3' month	Spontaneous delivery	No	No	Chorea disappears 4 months after pregnancy. 4 subsequent pregnancies without abnormalities
586	Gyn. Clinic, Malmö	1936	19	I	7' month	Spontaneous delivery	At the age of 5 years	No	Urine: no albumin. 2 subsequent pregnancies without abnormalities
672	General Hospital, Ystad	1930	19	I	—	Spontaneous delivery	—	No	2 subsequent pregnancies without abnormalities

came ill at the age of 21 or more, and that most of these patients were pregnant at the same time. Among 65 female choreic patients, 16—30 years old, Mühlbaum (1914) found 18 (27.9%) to be pregnant at the same time. Levine (1946) has not seen »a single instance of chorea occurring for the first time in a patient past the second decade, except in the rare instances when it is associated with pregnancy«. These findings indicate that chorea most likely is over-represented among pregnant women.

The present material throws some light on this question:

Considering the number of women of 20—34 years in Malmöhus county from 1910 to 1944 in relation to the number of cases of chorea in this age class (33 patients), the probability or risk of acquiring chorea for a woman in this age class is 1.5 per 100,000. When this ratio is applied to parturients in Malmöhus county in 1910—1944 we have a calculated value of 3—4 mothers with coincident chorea if the coincidence is due to accident alone. The number of coincidences of chorea and pregnancy in the age class mentioned is 12, however, and this means that the number of cases of chorea and pregnancy is 3—4 times greater than accident would give rise to.

So this material shows that the coincidence of chorea and pregnancy is not merely accidental. Pregnancy promotes the appearance of chorea. As to the pathogenesis of this coincidence, however, our knowledge is still defective.

Chorea in pregnancy may be a *recurrence of a previous chorea*, but every case is not a relapse. Among 38,382 obstetrical admissions Allard (1921) found 201 patients who gave a history of previous chorea, and now 53 of these patients had chorea in their pregnancy. On the basis of his studies, Allard thinks that a first appearance of chorea during pregnancy — chorée gravidique primitive — is very rare. This view, however, is in conflict with the observation reported by Kröner (1896) that in 126 cases of chorea in pregnancy only 48 patients gave a history of previous chorea. Further, Meumann (1912) found a recurrence of chorea only in 8 out of 15 cases of chorea in pregnancy.

To what extent pregnancy may influence the tendency to relapse present in most cases of chorea, however, is difficult to appraise numerically. In this respect the present material can offer no exact information, as it allows of no calculation of the risk of a choreatic relapse in the various age groups. Here it is merely to be mentioned that among the 18 cases of chorea in pregnancy 6 are established

with certainty to be relapses. In the compleutive follow-up examination 150 women gave an acceptable answer to the question whether they had had any recurrence of chorea in the subsequent pregnancy. These women had gone through 315 pregnancies, and 9 of them had been troubled with chorea — and only in one pregnancy. These figures appear to indicate that pregnancy promotes the occurrence of a choreatic relapse, but the figures are of such a character as to allow only of assumptions.

To what extent *rheumatic infection* is the cause of chorea in pregnancy is a question of the greatest interest — not least with reference to the prevailing view that »pregnancy lowers the susceptibility to rheumatism» (cited after Coburn, 1945). That the chorea encountered in pregnancy may be rheumatic chorea has been mentioned by various authors — e.g., Pineles (1913), who states that 17% of his patients previously had gone through an attack of acute polyarthritis, and who in 50 cases examined post mortem found 35 to show changes in the heart suggestive of rheumatic infection. Among 404 cases suitable for investigation as to the presence or absence of rheumatic infection, Willson & Preece (1932) found that the presence of rheumatic infection could be established in 167 cases (39.7%). The question as to what extent rheumatic infection is to be looked upon as the cause of chorea in pregnancy has been answered also by Jolly (1900), who says that in »Chorea gravidarum rheumatische und Herzaffektionen» occur at about the same rate as in chorea among adults in general.

In this respect, however, our material gives an answer divergent from the conclusion arrived at by Jolly. Among our 18 pregnant patients, aged 19—34, the chorea may be said with certainty in 7 cases to have been brought about by rheumatic infection, while among the remaining 25 women in the same age-class only 6 cases of rheumatic chorea were recorded. If this observation be correct — that rheumatic infection is the cause of chorea more often in pregnant women than in non-pregnant in the same age class — then rheumatic chorea will in this respect deviate from the prevailing picture of rheumatic infection.

The greatest interest concerning chorea in pregnancy is attached to the question whether chorea is an expression of a *toxemia of pregnancy* (e.g., Royston, 1921; Kehrer, 1942). This question is motivated not only by the coincidence of chorea and pregnancy but

also by the fact that this coincidence most often takes place in the beginning of pregnancy, above all, in the third month. Willson & Preece (1932) found that in half of all their cases the attack of chorea commenced in the 1'-3' month. But, as already mentioned, the onset of chorea is not limited to these three months but may happen in any of the 10 months. Furthermore, Willson & Preece have also reported 2 cases in which the chorea commenced with the parturition and 1 case in which it commenced on the second day post partum. Moreover, these authors have also reported that the average duration of the chorea after delivery was 22 days. Likewise, the findings reported by Kroner (1896) — that in 171 cases of this kind the chorea subsided prior to delivery in 47 cases, in connection with delivery in 30 cases and not till some time after delivery in 94 cases — make its interpretation as a possible stage of toxemia in pregnancy rather disputable.

In the present material the month for the onset of the chorea is known in 14 cases, namely:

Onset of chorea in		1' month of pregnancy	2 cases				
9	9	9	2'	9	9	9	1 case
9	9	9	3'	9	9	9	3 cases
9	9	9	4'	9	9	9	1 case
9	9	9	5'	9	9	9	1 9
9	9	9	6'	9	9	9	1 9
9	9	9	7'	9	9	9	4 cases
9	9	9	8'	9	9	9	1 case
9	9	9	9'	9	9	9	0 9
9	9	9	10'	9	9	9	0 9

In altogether 8 cases the onset happened within the first half of the gestation, and most of these within the first three months, while in 6 cases the chorea commenced in the second half of the period. In one case (No. 585) it has been ascertained that the chorea did not disappear until 4 months after the parturition, whereas in 2 other cases (Nos. 496 and 497) the chorea disappeared already before delivery, in the 6' and 3' months, respectively.

This observation in the literature and in the present material of the junctures of pregnancy for the onset and disappearance of chorea indicates that toxemia of pregnancy cannot be excluded altogether as a possible cause of the chorea. But the highly varying point of time for the appearance of the chorea makes it most likely that pregnancy is not the only cause. It may be that preg-

nancy is associated with the formation of certain products that lower the choreatic system to «the level of childhood» and that then the chorea-producing agents associated with that age may assert themselves (Wall, 1920).

Study of the clinical picture of chorea in pregnancy with its not infrequently violent course, with stronger psychic effect than in childhood has given rise to the idea that chorea in pregnancy often is brought about by a fulminant form of *encephalitis*, rather: epidemic encephalitis. An additional and stronger support of this view is found in the greatly increased mortality for chorea in pregnancy as compared to that for chorea in general. On this point, too, Willson & Preece have given some interesting information. They found the mortality for the patients to be 18.1%, for the state of pregnancy 15%. The mortality for chorea in general is considerably lower. In the present material, for instance, 13 out of 704 patients (1.9%) died during their hospitalization.

Willson & Preece have entered further into the question about encephalitis as a cause of chorea in pregnancy through a comparison between the mortality among the cases which could be said with certainty to be due to rheumatic infection in the course of pregnancy and the mortality for the entire material. Thus they were able to make the surprising statement that «there is a definitely lessened mortality in patients, who have had chorea or rheumatism previously and a still lower rate in those who had both». Thus among 135 pregnant women with a past history of rheumatism they found a mortality of 7.4% (10 deaths), and among 95 patients with a past history of chorea as well as «rheumatism» they found a mortality of 6.3% (6 deaths). A division of the material into age classes shows that the lowest mortality (13.7%) was to be found in the age group of 15—19 years, in which, according to our knowledge of the age-frequency curve for rheumatic infection, the probability of a coincidence of rheumatic chorea and pregnancy is greatest. In the age group of 20—24 years the mortality is 17.5%, and in the age group of 25—29 years it reaches the maximum of 20.4%. These figures show that the cause of the high mortality for chorea in pregnancy largely must be some morbid condition other than rheumatic infection. The clinical picture of the cases is strongly suggestive of a severe type of encephalitis. In this connection it may also be appropriate to mention that in his collation of 170

cases of pregnancy complicated by encephalitis, Roques (1928) found a mortality of 42%.

Naturally, the observations on chorea in pregnancy lead on to the question whether the chorea here signifies an increased susceptibility to encephalitis during pregnancy. It may be that the conditions here are analogous to those in acute anterior poliomyelitis to which an increased susceptibility during pregnancy now is taken as proved (Dhunér, 1944; Horstmann, Ipsen & Lassen, 1946). Concerning this point, further investigation is required. The present small material includes no unquestionable instance of epidemic encephalitis, even though one case (No. 567) presented diplopia and nystagmus, on which account the possibility of epidemic encephalitis has to be considered.

Obviously, then, the question about the cause of chorea in pregnancy is difficult to answer clearly. Undoubtedly, chorea in pregnancy is far more often caused by encephalitis — probably epidemic encephalitis — than is chorea in childhood. Also several other causes seem possible, and all of them have to be taken into consideration in the individual case. Further investigation of this question is required — but hampered by the relative scarcity of the lesion.

*Conclusion:* The present material includes 18 cases of chorea coincident with pregnancy among 477 female patients, making a frequency of 3.8%, giving rise to a discussion of the causes of chorea in pregnancy.

A mere accidental coincidence of chorea in pregnancy is no adequate explanation, as the material shows that chorea in pregnancy among women of 20 years or more is observed 3—4 times more often than might be expected from the probability of such a coincidence. In several cases the appearance of chorea in pregnancy represents a relapse of a previous chorea. Rheumatic infection is a not infrequent cause, and the present material indicates that possibly rheumatic infection is a more common cause of chorea in pregnancy than of chorea in non-pregnant women in the same age group. Toxemia in pregnancy may be an etiological factor as suggested by the circumstance that the appearance of chorea in pregnancy takes place chiefly in the first three months of pregnancy, but the occurrence of chorea in any month of pregnancy and its duration even long after the parturition rather suggests that a

possible toxemia of pregnancy is not the only cause. Encephalitis has been given as a common cause of chorea in pregnancy, and this view finds support especially in the high mortality for these cases, which is considerably higher than the mortality for the cases of chorea in pregnancy that are brought about by rheumatic infection.

In estimating the cause of chorea in pregnancy, as a rule, it is necessary in the individual case to consider several possible causes. Further investigation in this field is highly desirable — but rendered difficult by the relative scarcity of the lesion.

#### **Chorea from Uncertain Rheumatic Infection.**

In Chapter I an account is given of the criteria of rheumatic infection adopted for the present material, implying that at least two of the mentioned manifestations have to be observed in the given case before the presence of rheumatic infection may be looked upon as established. If only chorea is observed, its cause is considered uncertain. The etiology of chorea from uncertain rheumatic infection will therefore be the etiology in cases with chorea as the only morbid manifestation, and we meet directly with the questions as to what extent a rheumatic infection may be the cause in our 215 cases of cryptogenetic chorea.

The distribution of the established etiology in the present material — rheumatic infection in 467 cases, and some other form of known etiology in 22 cases — suggests at once that a majority of the 215 cases in the group of cryptogenetic chorea most likely had rheumatic infection.

The same is indicated by our knowledge of the fact that, like all other rheumatic manifestations (perhaps with the exception of erythema annulare), chorea initially may appear as a solitary morbid phenomenon. As early as 1850 Sée pointed out that chorea might be followed by arthritis. Poynton, Paterson & Spence (1920) hold that «the most frequent solitary manifestation of rheumatism is chorea». In their material of children under 12 years, these authors found chorea to be the initial manifestation in 33 cases, arthritis in 9, carditis in 5, and 2 or more simultaneous manifestations in 31 cases.

It is an experience established long ago, indeed, that chorea of obscure etiology on subsequent examination reveals its rheumatic character through the development of arthritis and, above all,

Table 10. *F. E. Batten's follow-up examination of choreic patients without previous signs of rheumatism. From the Hospital for Sick Children, Great Ormond Street, London. After The Lancet 1898, II, p. 1196.*

Date	No rheumatism		Rheumatism	
	No.	%	No.	%
On admission (from January, 1892, to June, 1894)	78	67.8	37	32.2
Three years later (July 1895)	65	56.5	50	43.5
Three years later (July 1898)	54	47	61	53

through the appearance of carditis. In Chapter II it is mentioned that the author has utilized this circumstance in order to complete the rheumatic chorea material. Several follow-up examinations of choreic patients have shown that the later this follow-up examination is carried out, the more instances of rheumatic manifestation may be observed. Follow-up studies on chorea have been reported by a good many authors — *e.g.*, Osler, 1887; Batten, 1898; Thayer, 1906; Forssner, 1910; Bertram, 1925; Hässler & Möller, 1932; Schwartz & Leader, 1935; Sutton & Dodge, 1938; Jacobsson, 1946. Here, I think, it will suffice to mention merely two of these reports: the paper by Batten who was the first to deal with the cases of monosymptomatic chorea as a group by itself, and the account published by Sutton & Dodge which is the most comprehensive and significant modern follow-up investigation of this kind.

Batten (1898) reported the outcome of his investigations as a tabulation, reproduced here in Table 10.

Batten examined a material of 115 cases of chorea, of which 78 (67.8%) proved at the first examination to show no signs of «rheumatism». These patients were reexamined after 3 and 6 years, and each time an increase was found in the number of patients with rheumatism.

Sutton & Dodge (1938), investigating a material of 1052 children, 467 of whom had chorea, had their patients under observation through 10 years and found, among other things, that in the 91 cases of initially monosymptomatic chorea it was possible to demonstrate the presence of heart disease in 10.5% after 3 years, in 15.1% after 6 years, and in 40% after 10 years.

A condition common to all follow-up examinations is that the outcome largely will depend on the initial material, the technique of examination and the interpretation of the findings. The results of

the various follow-up examinations therefore are subject to wide variations, but no investigator has found rheumatic manifestations in 100% of his cases. In some individuals, no doubt, chorea remains the only rheumatic manifestation throughout life.

So there is every reason to think that a majority of the cases in the group of cryptogenetic chorea have a rheumatic etiology. If we are to maintain the given criteria of rheumatic infection, however, we are unable in the individual case to say anything definite about the etiology. An increased sedimentation rate, fever, leukocytosis, relapsing tendency, acute suppurative tonsillitis, epistaxis, etc., may be suggestive of rheumatic infection, but a diagnosis on this basis will always be too uncertain.

Still, this survey of the various causes of chorea shows that chorea clinically may be brought about by different causes. Indeed, most critical authors agree that chorea *per se* should not be taken as a proof of rheumatic infection (*e.g.*, Gerstley *et al.*, 1935; Jones & Bland, 1935; Coburn & Moore, 1937; Usher, 1938; Sutton & Dodge, 1938).

*Conclusion:* Chorea may occur as a solitary symptom of rheumatic infection, which on subsequent examination reveals itself through the appearance of an additional rheumatic manifestation. All the follow-up examinations reported show that even though the number of rheumatic manifestations increases with increasing length of the observation period no investigator has yet found rheumatic infection present in every case on follow-up examination of patients with monosymptomatic chorea. As it has been described previously that the clinical picture of monosymptomatic chorea may be the same for several causes, chorea *per se* cannot be taken as proof of rheumatic infection even though this cause is the most common.

### 5. Discussion and Conclusion.

The survey given here of the etiology of chorea in the literature and in the present material shows that chorea may be brought about by several and widely different causes.

The rheumatic etiology is the most common. The etiological connection between chorea and rheumatic infection, however, is based entirely on the clinical coincidence of chorea and other

rheumatic manifestations in the same individual. Chorea occupies a special position among the manifestations of acute rheumatic infection. Here the sedimentation rate is usually low. Chorea appears to set in more often in pregnant women than in non-pregnant women in the same age class. Pathologic-anatomical studies and bacteriological investigations have not been able so far to offer any conclusive evidence of the rheumatic etiology of chorea. In this connection the reader may also be referred to Chapter V, in which it is pointed out that the age factor and sex factor in rheumatic infection occupy a special position in chorea.

So, for the present, the question as to whether the clinical connection between rheumatic infection and chorea also means an etiological connection will have to be left open. Until this question can be answered, however, it will be appropriate to look upon the clinical connection between chorea and rheumatic infection as representative of an etiological connection too. This means, of course, that the etiological connection which in this work is considered present under certain conditions really is a mere working hypothesis. Only further research into the cause of the rheumatic infection may substantiate the value of this hypothesis.

Identical clinical pictures of chorea may be produced by various agents other than rheumatic infection. Therefore, the appearance of chorea *per se* does not justify a rheumatic diagnosis.

The outcome of this survey of the etiology of chorea as reported in the literature and gathered from the present material may be expressed best by citing Coburn & Moore (1937), who say: »It is the authors' opinion that the physiological background prerequisite to the development of chorea may be prepared by a number of abnormal conditions but is especially well prepared by the rheumatic state.»

## CHAPTER V.

### Epidemiology of Chorea.

#### 1. Chorea in General.

The epidemiological aspects of chorea are stamped by the epidemiological factors applying to the causes of chorea. The most frequent cause of chorea will thus especially characterize the epidemiology of chorea. So, inasmuch as the rheumatic infection is the most common cause of chorea — in the present material of 704 cases of chorea rheumatic infection was unquestionably the cause of the chorea in 467 cases — it will, above all, be this disease that stamps the epidemiologic aspects of chorea.

In this connection, therefore, the epidemiology of chorea due to some cause other than rheumatic infection will be mentioned but quite briefly. Our material includes only 22 cases in which the cause of the chorea is known not to have been rheumatic infection. It hardly needs mention that chorea brought about by birth injury asserts itself early in life, whereas chorea due to arteriosclerosis or arterial hypertension does not manifest itself until later in life. Degenerative hereditary chorea, as mentioned before, makes its appearance chiefly at middle age, while chorea due to various infectious diseases makes its appearance in the age classes where these diseases are found.

These 22 cases are not conspicuous in the epidemiological aspects of chorea in general, except where the incidence of rheumatic infection is insignificant. This happens, above all, in the age group over 30 years. In Table 11, where the age at first admission to hospital for chorea is recorded, and in which the number of patients of 30 years or more amounts to 15, the chorea was found in 9 cases to be due to some cause other than rheumatic infection. The mean age for the entire material is 12.2 years, and for the group of chorea of non-rheumatic origin it is 28 years.

Table 11. *Age at first admission to hospital for chorea in Malmöhus county 1910—1944.*

Age in years	Entire material		
	Males	Females	Total
0— 1	0	0	0
1— 2	0	0	0
2— 3	0	0	0
3— 4	0	3	3
4— 5	4	10	14
5— 6	8	7	15
6— 7	11	22	33
7— 8	17	33	50
8— 9	38	36	74
9—10	24	54	78
10—11	27	49	76
11—12	18	60	78
12—13	19	44	63
13—14	20	25	45
14—15	10	30	40
15—16	7	16	23
16—17	4	18	22
17—18	5	12	17
18—19	2	8	10
19—20	3	10	13
20—21	3	10	13
21—22	0	4	4
22—23	1	6	7
23—24	0	2	2
24—25	1	2	3
25—26	1	0	1
26—27	0	2	2
27—28	1	1	2
28—29	0	0	0
29—30	0	1	1
30—31	0	1	1
31—32	0	1	1
32—33	0	1	1
33—34	0	1	1
34—35	0	1	1
35—36	0	0	0
36—37	0	1	1
37—38	0	0	0
38—39	0	1	1
39—40	0	0	0
40—>	3	5	8
Total	227	477	704

Concerning the epidemiological aspects of chorea, however, the interest is attached exclusively to these aspects of rheumatic chorea.

## 2. Rheumatic Chorea.

### Introductory Survey.

Chorea as a rheumatic manifestation represents merely a part of the epidemiology of acute rheumatic infection, which is indeed a summation of the epidemiological aspects of all the rheumatic manifestations. Therefore, in order to appreciate the epidemiological aspects of rheumatic chorea, it is essential to be acquainted with the epidemiology of rheumatic infection on the whole.

The epidemiology of the rheumatic infection has long attracted considerable interest, but the many rheumatic manifestations and their varying features in the different age-classes have made it difficult to survey. As early as 1889 Cheadle said: »In the rheumatism of early life arthritis is at its minimum; endocarditis, pericarditis, chorea, and subcutaneous nodules at their maximum. As life advances, this is gradually reversed; the joint affection becomes prominent, constant and typical of the disease and reaches its maximum; while the other phenomena decline and tend to die out.»

Not until the last decades, however, has it been possible for rheumatic research to give a numerical expression of the experiences mentioned by Cheadle. Above all, since recently it has been realized that the major epidemiological rôle of the rheumatic infection falls in childhood — a thing that was realized at the same time as the carditis was assigned the central position in the rheumatic complex — it has become practicable to obtain a fairly accurate survey of the rheumatic epidemiology in its entire extent. Previously, it was almost exclusively the epidemiological aspects of the rheumatic arthritis that stamped our conception of the epidemiology of rheumatic infection.

Investigations concerning all the rheumatic manifestations in all age classes, which thus could be taken as representative of the epidemiology of rheumatic infection, are still few in number and incomplete with regard to all epidemiological details.

Ritchie (1935) has given a diagrammatic survey of the age at the onset of clinical manifestations of »acute rheumatism» in Edinburgh, comprising 244 cases in all age-classes, 60 of which were associated with chorea. In this not quite representative material he finds the onset of illness most frequent in the age class of 11—15 years.

Hedley (1940) has contributed most to our present knowledge about the epidemiology of rheumatic infection through his studies on 4538 cases of rheumatic heart disease, rheumatic fever and Sydenham's chorea referred to Philadelphia hospitals from January 1, 1930 to December 31, 1934. He has taken all the more important rheumatic manifestations into consideration, also all age-classes, and he has carried out his investigation on such a large scale that it has to be looked upon as representative of the acute rheumatic infection.

The relation between the different rheumatic manifestations is indicated by the fact that he found rheumatic heart lesions in over 80% of the cases, rheumatic fever (arthritis) in nearly 30% and Sydenham's chorea in a little over 15%. The percental distribution of these manifestations in all age-classes differs widely, however. Thus 97.1% of all the cases of chorea were found in patients under 20 years — as against 59.6% of cases of rheumatic fever, and 47.8% of patients with rheumatic heart lesions.

The peak of the age at onset of rheumatic infections falls in Hedley's material at 8—9 years. The average age at the onset of rheumatic fever was 8.7 years, of rheumatic heart disease 8.9, and of Sydenham's chorea 9.3 years.

The sex distribution for rheumatic fever was 49.9 males and 50.1 females; for rheumatic heart disease it was 43.6 males and 56.4 females, and for chorea it was 34.7 males and 65.3 females.

Jacobsson (1946), who also took into account the more important manifestations and all age-classes, has presented some of the epidemiological problems of the acute rheumatic infection through studies on a material from hospitals in Gothenburg, comprising 1991 cases of «rheumatic fever with chorea minor».

In Jacobsson's material the peak of the age at onset of rheumatic infection falls for male patients at 9 years, for females at 10 years. Of all initial attacks of rheumatic infection, 49.5% occurred before the age of 20; and of all the initial attacks of chorea only one commenced after the age of 20 years. The age of predilection for the onset of chorea was found to be 7—12 years.

The sex distribution for the entire material was 872 males (43.85%) as against 1119 females (56.15%). For the cases of chorea it was 29.5% males and 70.5% females.

Jacobsson investigated at the same time a material of children from the Children's Hospital in Gothenburg, in which the relative

frequency of the different initial rheumatic manifestations proved to be: arthritis 75.6%, chorea 18.4%, and carditis 5.95%.

In connection with an investigation covering 48 000 children, concerning the effect of tonsillectomy with rheumatic infection, Kaiser (1927) makes a statement of epidemiological value with regard to rheumatic infection. Among the 28 000 non-tonsillectomized children he found joint complaints in 3%, carditis in 2.9% and chorea in 0.5%.

These investigations are the ones that have been of greatest importance to our present conception of some of the epidemiological aspects of rheumatic infection, and a summarizing recapitulation of them gives us in brief outline the following picture:

Of the three most common manifestations of the rheumatic infection — carditis, arthritis and chorea — taking all age-classes into account, chorea is the least frequent. The relative ratios of the manifestations mutually vary with the age-classes. Of all the cases of rheumatic infection about one-half sets in before the age of 20, but nearly all initial attacks of chorea occur before this age. The first attack of rheumatic infection is most common at the age of 8—10 years, the initial attack of chorea occurs most often at the age of about 10 years. Chorea is the rheumatic manifestation in which the age factor asserts itself most conspicuously.

The sex distribution for acute rheumatic infection shows somewhat lower figures for males than for females. Chorea is the rheumatic manifestation in which the number of male patients in proportion to females is lowest.

#### Sex Distribution.

Of the 467 patients with rheumatic chorea in the present material, 150 are males, 317 females. The group of cryptogenetic chorea comprises 215 patients, 70 males and 145 females. Thus we have

the quotient of males/females for rheumatic chorea	1:2.11,
»   »   »   »   »   »   »   cryptogenetic chorea	1:2.07,
»   »   »   »   »   »   »   both groups together	1:2.10.

As the sex distribution for the population of Malmöhus county, calculated from the censuses in the period covered by this investigation for all the age-classes is 1:1.07, it is obvious that here the

incidence of rheumatic chorea is about twice as high for females as for males.

A comparison of these figures with the results from other chorea materials comprising *all age-classes* as reported in the literature shows on the whole a very good agreement, even though the presupposition of the materials has not been the same.

Mackenzie (1887), reporting a material comprising 439 individuals of all ages and chorea of varying origin, found a sex distribution of 1 male:2.8 females.

Wollenberg (1899), collating 21 reports on infectious chorea covering altogether 3595 cases, found a sex distribution of 1:2.2, varying from 1:1.3 to 1:3.3.

Thayer (1906), studying 808 cases of chorea, found 1:2.48.

Wall (1920), working with a material mostly like the present, found among 278 first attacks of chorea 81 males and 197 females, giving a quotient of 1:2.42.

Hedley (1940) found for 687 cases of »Sydenham's chorea« in all age-classes 34.7% males and 65.3% females (1:1.88).

The sex distribution for materials of *children* has been reported from many places. Here only some results will be given for previous investigations carried out in Sweden.

Nordgren (1923), working up a material from all the children's hospitals in Stockholm, found 125 boys and 218 girls (1:1.74).

Faxén (1933), investigating 117 cases from the Children's Hospital in Gothenburg, reports a sex distribution of 1:2.60.

Karlström (1940), examining 410 chorea minor patients from the same hospitals as Nordgren's material, found 123 boys and 287 girls (1:2.33).

Jacobsson (1946), working with a material of 127 chorea minor patients from the Children's Hospital in Gothenburg, found 39 boys and 88 girls, giving a quotient of 1:2.26.

For the sake of comparison with these materials of children, in the present material I have calculated the sex distribution for the age group of 0—14 years, in which the group of rheumatic chorea was found to show a sex distribution of 1:1.94, while the group of rheumatic chorea + cryptogenetic chorea — in which the monosymptomatic rheumatic chorea has a chance of asserting itself — gives a quotient of 1:1.86.<sup>1</sup>

<sup>1</sup> The sex distribution for the age group of 0—14 years in the population of Malmöhus county, calculated after the censuses, gives a quotient of 1:0.97.

**Table 12.** *Sex distribution of rheumatic manifestations observed in the history or state of the patients at first hospitalization for rheumatic infection in 578 children aged 0—14 years, in the Pediatric Clinic in Lund 1910—1944.*

Rheumatic manifestation	Male No.	Female No.	Total No.	Male/Female
Chorea	42	82	124	1 : 1.95
Arthritis	176	130	306	1 : 0.74
Carditis	212	189	401	1 : 0.94
Nodules	2	3	5	
Erythema annulare	2	2	4	
Erythema nodosum (tuberculin-negative)	5	5	10	
Total	439	411	850	1 : 0.94
Individuals of 0—14 years in the material	289	289	578	1 : 1.00
Individuals of 0—14 years in the population (total of 5 censuses)	314 657	304 923	619 580	1 : 0.97

A comparison between the sex distribution in rheumatic chorea and in the other rheumatic manifestations is mentioned already in the introduction to this chapter. Only a few statements of this kind are to be found in the literature (Campbell & Warner, 1930; Hedley, 1940; Jacobsson, 1946), and no material is quite comparable with the present material because of differences in the definition of rheumatic infection.

In order to obtain a material as far as possible comparable with the present, showing the sex distribution in rheumatic chorea in proportion to that observed in the other rheumatic manifestations, the author has gathered the first visit cases of acute rheumatic infection treated in the Pediatric Clinic in Lund during the same period as covered by the chorea material and estimated after the same diagnostic criteria as employed for the chorea material. This material comprises 578 children. The rheumatic manifestations observed on first admission for rheumatic infection are distributed after sex, and the result is recorded in Table 12.

In this table the last column gives the male/female quotient. It will be noticed that the population in the age class of 0—14 years comprises more boys than girls, but the number of patients treated for rheumatic infection is exactly the same for the two sexes. This implies that in the period here concerned the rheumatic infection appeared in somewhat more girls than boys. Considering the total number of rheumatic manifestations, we find that, taking the same number of boys and girls, the boys have somewhat more manifestations of their rheumatic infection than have the girls. As to the sex distribution of the various manifestations, arthritis and carditis are diagnosed more often in the boys, chorea and skin manifestations more often in the girls. Arthritis is relatively more common in the boys, chorea more common in the girls. Among the various manifestations the difference in sex distribution is greatest for chorea.

*Recapitulation:* In the present material the sex distribution, male/female, covering all age-classes, is 1:2.11 for rheumatic chorea, 1:2.10 for rheumatic chorea + cryptogenetic chorea. In the population the sex distribution is 1:1.07.

In the age group of 0—14 years the corresponding figures are 1:1.94 and 1:1.86, and for the population 1:0.97.

On comparison with the age distribution for all the rheumatic manifestations in a material of acute rheumatic infection in the age group of 0—14 years it is evident that chorea is the rheumatic manifestation in which the sex difference asserts itself most conspicuously. Here the sex distribution is 1:0.74 for arthritis, 1:0.94 for carditis, 1:1.11 for skin manifestations, and 1:1.95 for chorea.

#### **Age Distribution.**

The significance of age to the appearance of chorea was noticed already by Sydenham who in his classical description pointed out that chorea was observed chiefly in children between 10 and 14 years of age. Nowadays, the significance of the age-class to the development and character of the rheumatic infection on the whole is realized. In the introduction it is also mentioned that among the various manifestations of rheumatic infection chorea is the one in which the age factor asserts itself most clearly.

Table 13. *Age at onset of the first attack of rheumatic chorea and cryptogenetic chorea with regard to the sex distribution.*

Age in years	All cases			Rheumatic chorea			Cryptogen. chorea		
	M.	F.	Total	M.	F.	Total	M.	F.	Total
0—1	0	0	0	0	0	0	0	0	0
1—2	0	0	0	0	0	0	0	0	0
2—3	0	1	1	0	0	0	0	1	1
3—4	0	5	5	0	2	2	0	3	3
4—5	4	12	16	3	8	11	1	4	5
5—6	8	10	18	4	7	11	4	3	7
6—7	12	22	34	10	16	26	2	6	8
7—8	17	31	48	12	18	30	5	13	18
8—9	34	38	72	24	27	51	10	11	21
9—10	21	46	67	19	37	56	2	9	11
10—11	21	43	64	12	33	45	9	10	19
11—12	20	51	71	15	31	46	5	20	25
12—13	20	35	55	14	30	44	6	5	11
13—14	14	17	31	11	13	24	3	4	7
14—15	7	22	29	3	17	20	4	5	9
15—16	5	15	20	4	9	13	1	6	7
16—17	3	11	14	3	8	11	0	3	3
17—18	5	12	17	3	9	12	2	3	5
18—19	2	6	8	2	4	6	0	2	2
19—20	2	7	9	2	3	5	0	4	4
20—21	1	5	6	1	3	4	0	2	6
21—22	0	3	3	0	2	2	0	1	1
22—23	1	2	3	1	1	2	0	1	1
23—24	0	1	1	0	1	1	0	0	0
24—25	0	0	0	0	0	0	0	0	0
25->	1	5	6	0	3	3	1	2	3
Total	198	400	598	143	282	425	55	118	173

In the material of rheumatic chorea it has been possible to establish the age of the patient at the first appearance of chorea in 425 cases, 143 males and 282 females. In the group of cryptogenetic chorea the corresponding figures are 173 patients, 55 males and 118 females. In Table 13 these 598 cases are grouped after the character of chorea — rheumatic and cryptogenetic — and also after age and sex.

The frequency curve plotted from the data in Table 13 for rheumatic chorea is presented in Fig. 5, and the frequency curve for rheumatic chorea+cryptogenetic chorea is shown in Fig. 6. Both these graphic presentations were considered essential to give a representative picture of the age distribution for chorea in rheumatic infection, as neither curve is quite representative of chorea in rheumatic infection. For the rheumatic chorea material does not include the cases of monosymptomatic rheumatic chorea, which are found in the cryptogenetic group; the latter, however, includes also cases of other unknown etiology.

The frequency curve for rheumatic chorea (Fig. 5) shows a relatively rapid and gradual rise to the apex, at the age of 9 years. Then it falls and at the age of 10—13 years it shows an almost even plateau, after which it falls rather abruptly to the age of 16, whereafter it declines slowly — at a considerably smaller angle than that of the ascending limb. This is a frequency curve with negative obliqueness, the youngest age being 3 years, the highest 32. The typical age for the first appearance of rheumatic chorea is 9 years, while the mean age is 10.6 years.

On studying the frequency with regard to the sex of the patients, some differences turn up. In all age-classes the female patients are more frequent than the male; they turn up earlier and later than the males, but their type age is as high as 9 years, while for the boys the type age is 8 years. The mean age for the female patients is 10.8 years, for the males 10.1.

Table 14 shows the material distributed after sex and in hemidecades. This shows that the boys get chorea mostly in the second hemidecade, the girls in the third hemidecade. Before the age of 15 years no less than 89% of the boys had their first attack of chorea as against only 85% of the girls. From the age of 20 years 1.4% of the patients are males, 3.9% females. Of the male patients only 2 had the first onset of chorea at the age of 20 or more, whereas 10 women fall in this age group. In 4 of these cases the chorea appeared in connection with pregnancy.

The frequency curve for rheumatic chorea+cryptogenetic chorea (Fig. 6) shows in some respects a course different from that of the frequency curve for rheumatic chorea alone. It shows two distinct peaks — one at the age of 8 years, the other at 11 years, which corresponds to the typical age for the male patients (8 years) and

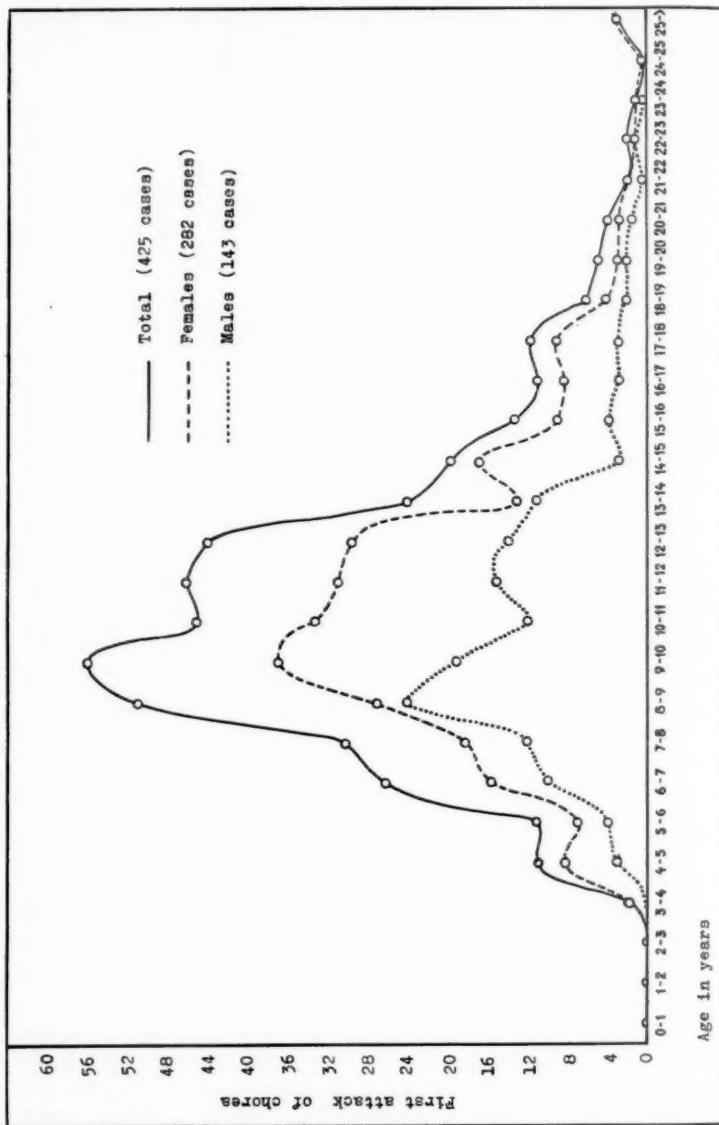


Fig. 5. Age at onset of first attack of rheumatic chorea.

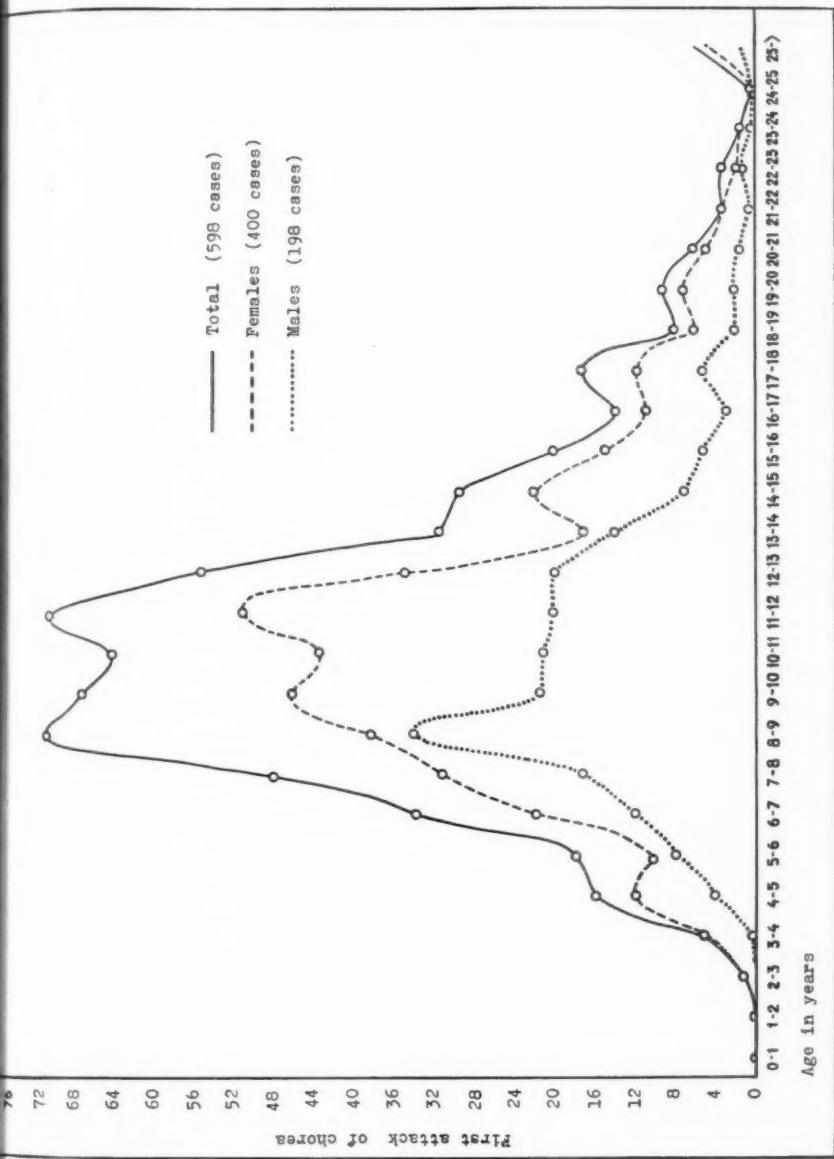


Fig. 6. Age at onset of first attack of rheumatic chorea (425 cases) and cryptogenic chorea (173 cases).

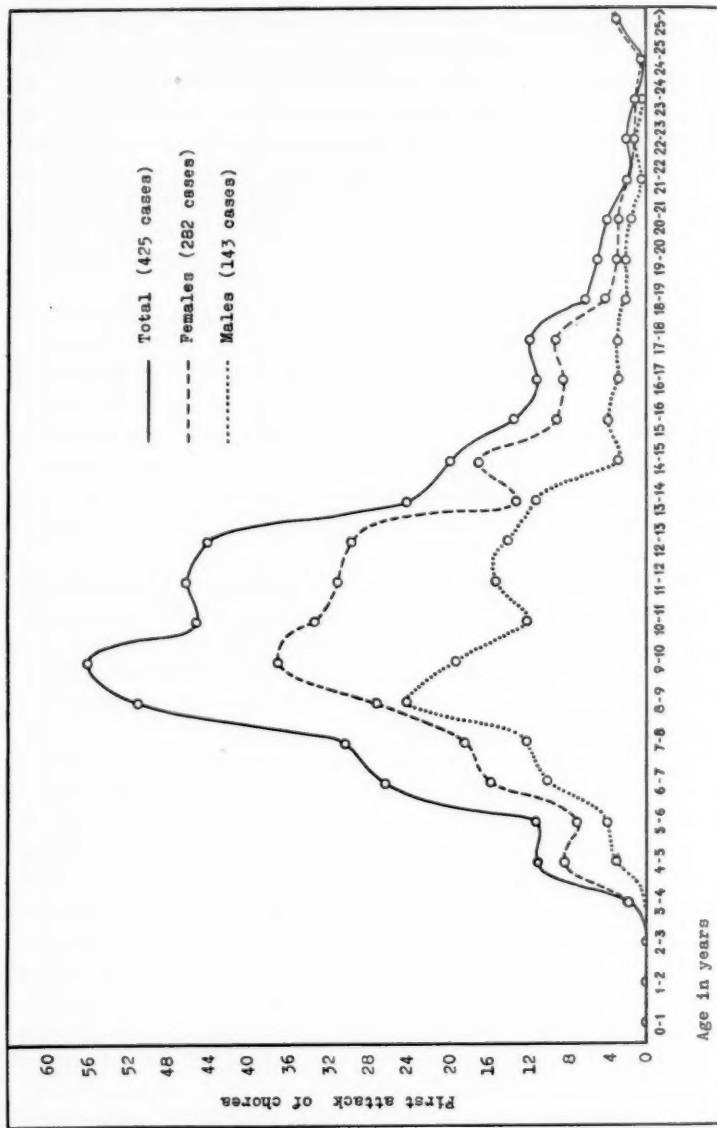


Fig. 5. Age at onset of first attack of rheumatic chorea.

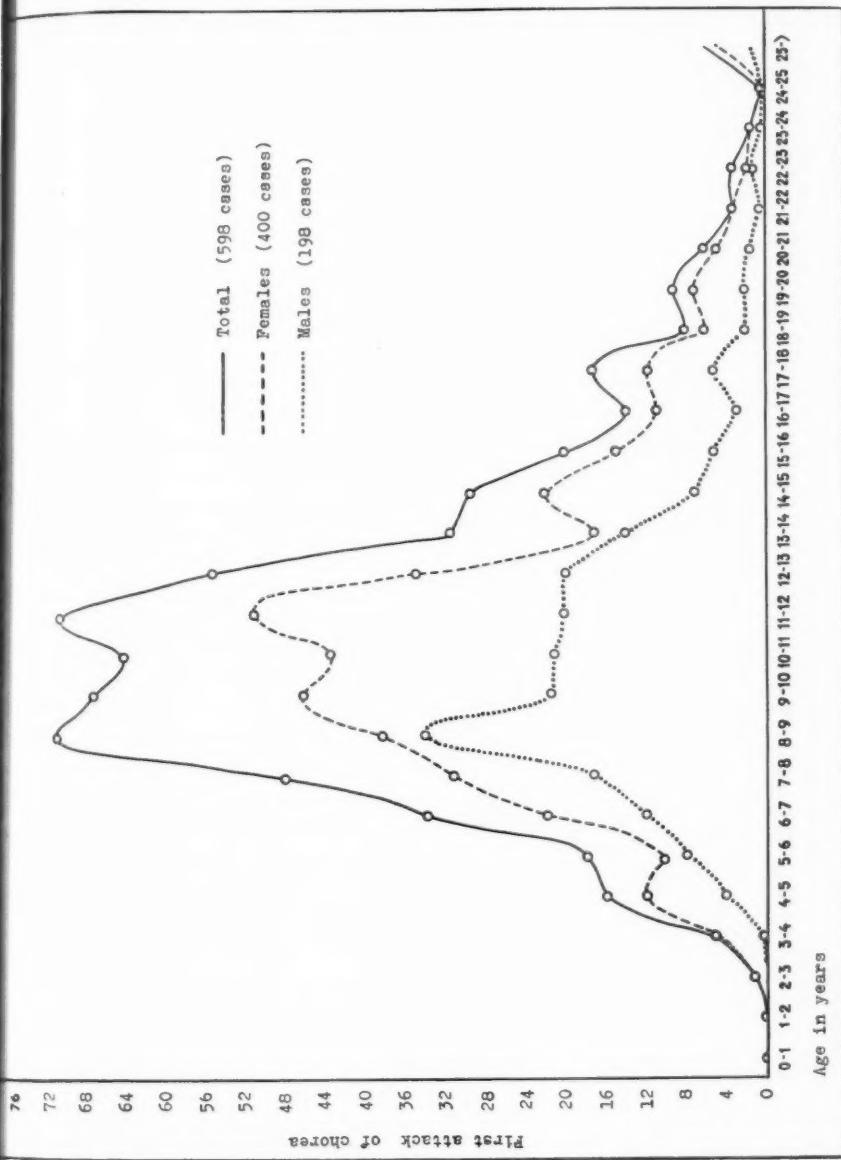


Fig. 6. Age at onset of first attack of rheumatic chorea (425 cases) and cryptogenic chorea (173 cases).

Table 14. *Age at onset of first attack of rheumatic chorea distributed on hemi-decades and after sex.*

Age in years	Total		Males		Females	
	No.	%	No.	%	No.	%
0—4	13	3.1	3	2.1	10	3.6
5—9	174	40.9	69	48.1	105	37.2
10—14	179	42.1	55	38.5	124	44.0
15—19	47	11.1	14	9.8	33	11.7
20—24	9	2.1	2	1.4	7	2.8
25->	3	0.7	0	0	3	1.1
Total	425		143		282	

for the females (11 years). Thus the typical age for female patients shifts from 9 years in the rheumatic chorea material to 11 years in the combined material. This change in the frequency curve, however, is too insignificant to allow of any conclusion concerning an etiological factor in the group of cryptogenetic chorea associated with the female sex and the age of 11 years.

The chorea literature has brought many statements concerning the age distribution in chorea, but as a rule they refer to materials of children, and they do not always give the criteria employed for the diagnosis of rheumatic infection. Often the data have been obtained on first admission to the hospital.

Among investigations reported in the preceding century, which do not take into account the rheumatic etiology alone, mention may be made of that of Mackenzie (1887) who worked up a material of 439 cases of chorea in all age-classes, in which he found an initial onset at 5—10 years in 34%, at 10—15 years in 43%, at 15—20 years in 16%, and at 21 years or more only in 4—5%. Osler (1894) reported 392 cases of chorea, among which only 1.4% were over 20 years. Over three-fourths of the cases occurred in the second and third 5-year periods.

In this century, Wall (1920) has reported an investigation from London, comprising 278 first attacks of chorea, among which 245 (or more than 88%) appeared at the age 5—15 years, and in all the cases but four it appeared before the age of 21. From Edinburgh Wallace (1933) has reported a chorea material of 200 cases, comprising all ages, in which he found the mean age of the patients on admission to the hospital to be 11.7 years for the males, 13.4 years for the females; 6.6% of the cases in boys occurred after the age of 16 years, 14.5% of the cases in girls.

Table 15. *Age distribution of various materials.*

Age in years	Percentage of cases		
	Thayer (808)	Hedley (920)	Present material (425)
0—4	2.5	5.8	3.1
5—9	38.4	51.2	40.9
10—14	46.2	37.6	42.1
15—19	10.4	3.7	11.1
20->	—	1.8	2.8

Thayer (1906) and Hedley (1940) have reported the materials most comparable with the present material of rheumatic chorea. A comparative survey of the age distribution for these three materials in the various age-classes is given in Table 15.

Thayer has recorded the age of the patients on admission to the hospital; Hedley, like the present writer, gives the age of the patients at the first appearance of chorea. But the respective authors have not adopted the same criteria for rheumatic infection. Nor is the concordance of the percental distribution in the various age-classes quite identical in these materials from Baltimore, Philadelphia and Malmöhus county. But the tendency of the figures is the same in the three materials: a majority of all cases of rheumatic chorea appear at an age between 5 and 15 years, this lesion being rare before the age of 5 years and after 20.

In the chorea literature greater interest has been taken in the establishment of the youngest cases of rheumatic chorea than in the oldest ones, which is in keeping with the attention paid to rheumatic infection in general. It is a perplexing fact that the individuals have to grow up in order to become rheumatic. But every report of an instance of rheumatic chorea in a child under 3 years has to be accepted only with a great deal of criticism, partly because there is a weft of chorea in the motility of little children — the younger the child, the more pronounced is this feature (Homburger, 1923) — partly because other causes of chorea (*e.g.*, birth injury) are more common in the first two years of life than is rheumatic infection.

The youngest case of unquestionable rheumatic chorea appears to have been reported by Campbell & Warner (1930) who in their studies on 250 children with rheumatic disease in London found the earliest attack of chorea to have occurred at the age of 18 months. The youngest case of rheumatic chorea verified pathologic-anatomically has been reported by Schroeder (1925). This patient was a girl, 20 months old, in whom the autopsy revealed rheumatic endocarditis and pericarditis.

In the present material of rheumatic chorea the youngest age among the girls is 3 years (Cases 77 and 366), while the youngest among the boys is 4 years, at which age 3 boys had their first attack (Cases 232, 282, and 439). The highest age among the women for the first attack of chorea is 32 years (Case 302, a pregnant woman), while the highest age for the men is 22 years (Case 200, a man with arthritic joint complaints 7 years before, but well since).

With reference to the epidemiology of rheumatic infection, however, it is not of particularly great interest to establish the earliest age for the appearance of rheumatic chorea, as all investigators who have occupied themselves with the various rheumatic manifestations in the first years of life agree that there are more cases of arthritis in infancy than of chorea.

*Recapitulation:* The typical age for the first onset of rheumatic chorea in a material of 425 patients is 9 years, the mean age 10.6 years. For the male patients the typical age is 8 years, and for the females it is 9 years, while the mean age for the males is 10.1 years, for the females 10.8 years. The youngest age at onset is 4 years for the boys, 3 years for the girls; the highest age is 22 years for the men, 32 years for the women. Of the total patient material 86% had their first onset of rheumatic chorea before the age of 15 years, only 3% at the age of 20 or more. For the male patients the corresponding figures are 89% and 1%; for the females 85% and 4%.

Reckoning the group of cryptogenetic chorea together with the group of rheumatic chorea gives a total of 598 cases of chorea. The frequency curve for this total shows the same typical age for the males as in the group of rheumatic chorea alone (8 years), while the typical age at the onset for the female patients shifts from the age of 9 years to 11 years.

### Annual Variation.

An annual variation of the rheumatic infection was pointed out early, chiefly through studies on rheumatic arthritis (*e.g.*, Hirsch, 1860; Newsholme, 1895), and has been reported from various countries — from Sweden by Edström (1935), from Denmark by Warburg (1931), from Norway by Motzfeldt (1934), from England by Greenwood & Thompson (1908), and from U.S.A. by Seegal & Seegal (1927), Atwater (1927) and others. All these investigators found marked variations in the annual frequency of the lesion, with a certain degree of periodicity. Thus, Edström (1935) was able to demonstrate pronounced maxima in 1904—1905, 1915—1916, 1920—1922 and 1929—1932, with minima in 1913, 1918 and 1924.

A cyclic annual variation similar to the one observed in rheumatic arthritis has been reported also in chorea, especially from Sweden. Thus Nordgren (1923) was able in a material of 343 cases of chorea from all the children's hospitals in Stockholm in 1908—1921 to show not only that there was an annual variation in the frequency of the chorea but also that this followed the annual variation in a rheumatic material without chorea, comprising 369 cases. He ascertained the number of cases from July 1 to the following June 30, and found an increased frequency of chorea in 1908—1909, 1910—1911, 1912—1913 and 1919—1921, while the lowest frequency was recorded for 1909—1910 and 1918—1919.

Karlström (1940) has correlated the cases of »chorea minor» and acute polyarthritis admitted to all the children's hospitals in Stockholm in 1920—1939. He does not occupy himself particularly with the annual variation in the frequency of chorea, it is true, but such a variation is evident from his tabulations. These show the highest frequency of chorea in 1920—1922, 1926, 1930, and 1937; and, as a rule, the years showing an increased frequency of polyarthritis show also more cases of chorea among the children.

Jacobsson (1946) has reported the annual variation for all the children with chorea, arthritis or carditis in the Gothenburg Children's Hospital during the period of 1922—1942 with regard to the initial attack. Among 726 cases he found a maximal frequency for 1930, 1934 and 1939, a minimal frequency for 1924, 1931, 1935, and 1941. The number of choreic patients in his material is 129, and

Table 16. Distribution after years of first onset of rheumatic chorea and cryptogenetic chorea in Malmöhus county 1910—1944.

Calendar year at onset	Rheumatic chorea	Cryptogen. chorea	Total
1910	13	8	21
1911	16	4	20
1912	27	10	37
1913	18	12	30
1914	12	4	16
1915	15	4	19
1916	13	6	19
1917	8	3	11
1918	5	7	12
1919	9	5	14
1920	16	1	17
1921	23	8	31
1922	15	8	23
1923	8	11	19
1924	10	6	16
1925	11	6	17
1926	13	4	17
1927	18	4	22
1928	16	4	20
1929	16	5	21
1930	17	4	21
1931	19	5	24
1932	11	7	18
1933	12	6	18
1934	8	9	17
1935	9	5	14
1936	7	0	7
1937	7	4	11
1938	11	3	14
1939	4	4	8
1940	6	6	12
1941	6	2	8
1942	3	3	6
1943	10	0	10
1944	7	2	9
Total	419	180	599

this is too small to allow of any correct comparison of the various years. Still, it is to be noted that he found most initial attacks of chorea in 1922, 1927, 1930, 1932, and 1938—1939.

As far as I have been able to find out, no investigation has been reported from other countries comparable to these studies of chorea from Sweden. From Munich, Peters (1939) has briefly reported the annual variations in the number of choreic patients during

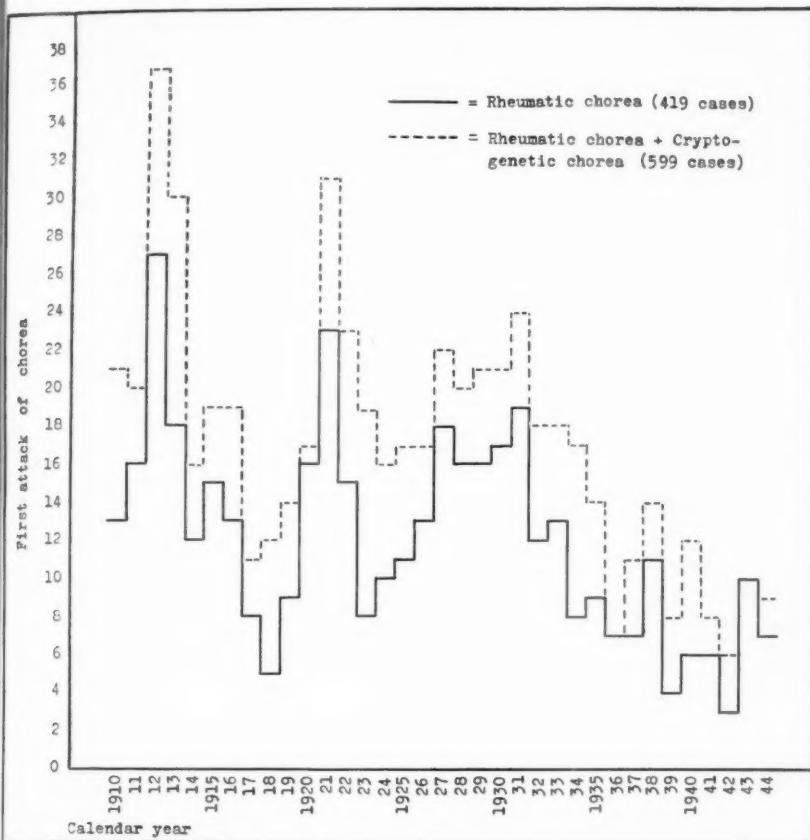


Fig. 7. Graphic presentation of distribution after years of cases of chorea as recorded in Table 16.

the period of 1923—1938, finding »chorea minor« to have been particularly frequent in the winters of 1925/26, 1928/29 and 1931/32.

On the background of these investigations it will be of interest to look into the annual variations in the present material. In Table 16 the figures are recorded for the cases of rheumatic chorea (419) and cryptogenetic chorea (180) in which the year of the first attack of chorea could be given with certainty. Fig. 7 shows the annual

Table 17. Distribution after years of 578 initial attacks of acute rheumatic infection (arthritis, carditis, chorea, nodules, erythema annulare, tuberculin-negative erythema nodosum) in the Pediatric Clinic in Lund 1910—1944.

Calendar year at onset	Acute rheumatic infection	Calendar year at onset	Acute rheumatic infection
1910	16	1928	13
1911	23	1929	18
1912	29	1930	11
1913	20	1931	14
1914	15	1932	18
1915	17	1933	12
1916	14	1934	20
1917	12	1935	15
1918	6	1936	10
1919	11	1937	20
1920	17	1938	19
1921	19	1939	27
1922	7	1940	33
1923	10	1941	17
1924	12	1942	12
1925	5	1943	33
1926	8	1944	36
1927	9	Total	578

distribution of rheumatic chorea, and of rheumatic chorea+cryptogenetic chorea in 1910—1944.

The rheumatic chorea material contains only cases in which rheumatic infection has been the cause of the chorea — according to the criteria given in Chapter I. Undoubtedly the group of cryptogenetic chorea includes several cases in which chorea has been the only symptom of rheumatic infection. In order to obtain the best representative picture possible of the annual variation of rheumatic infection as manifest in chorea, therefore, both of these materials have been taken into consideration. On comparison of the graphical presentation of the two materials, however, their difference in annual fluctuations is seen to be so slight that it will be sufficient in the following only to consider the graphical presentation of rheumatic chorea.

Fig. 7 shows the quite distinct annual variation in this material as far as the first attacks of chorea of rheumatic etiology are concerned. A maximal frequency of the lesion is found for 1912, 1921, 1931 and 1938; the longest interval between these maxima is

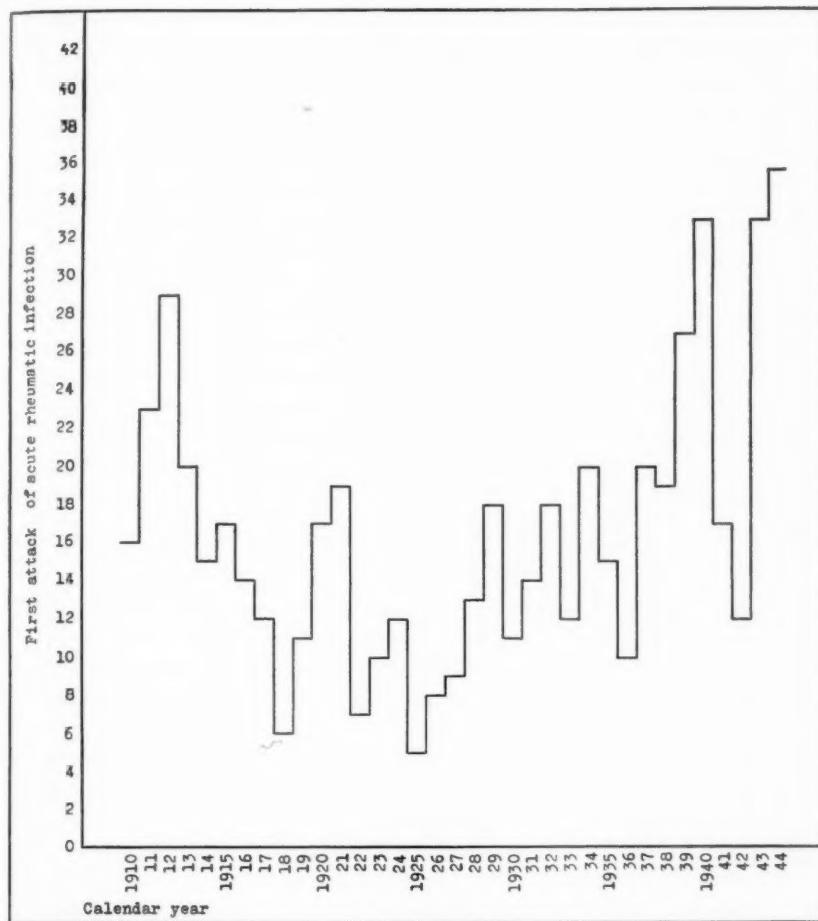


Fig. 8. Distribution of the first attack of acute rheumatic infection (578 cases) as recorded in Table 17.

10 years, the shortest 7 years. A minimal frequency of the lesion is recorded for 1918, 1923, 1936 and 1942; and the longest interval between the minima is 13 years, the shortest 5 years. These figures show an annual variation in the frequency of the initial onset of

rheumatic chorea as well as a certain degree of periodicity. But the latter features show no regular cyclic course.

On comparison of the present material with previous investigations reported from Sweden concerning maxima and minima in the various chorea materials, we find a fair degree of concordance with Nordgren's material as well as with the material reported by Karlström and Jacobsson. This concordance shows that there can be no doubt about the periodical factor asserting itself in the occurrence of rheumatic chorea.

On comparison between the annual variation in the incidence of rheumatic chorea and in other rheumatic manifestations as reported from Sweden by Edström (1935) and Jacobsson (1946) we find largely the same tendency to annual variations in the various materials.

In order to obtain the most comparable material with regard to the criteria adopted and the period concerned, I have investigated the aforementioned material of first visit cases of acute rheumatic infection admitted to the Pediatric Clinic in Lund within the period of 1910—1944 with regard to the year for the commencement of the rheumatic infection. The year for the initial onset of the rheumatic infection could be established in 578 cases and the yearly distribution of these cases is evident from Table 17 and Fig. 8.

Comparison of Fig. 7 and Fig. 8 shows a high degree of parallelism in the annual variations of the two materials during the first decade and the greater part of the second decade. But this does not apply to the last 15 years, when the incidence of rheumatic infection shows an increased frequency and irregular annual variation. Certainly the reason for this difference is to be looked for in the circumstance that during the last 15—20 years there has been an increasing understanding of the rheumatic infection in children, supported by laboratory examinations, physical and roentgenological methods for examination of the heart and by the health control in the schools, and this has increased the hospitalization of rheumatic patients in such a degree that the annual variation of the disease becomes conspicuous only in the choreic manifestation, for which the criteria largely have been the same.

A similar increased hospitalization, commencing about 1925, has been reported by Edström (1935) for acute rheumatic polyarthritis in all the hospitals in Sweden. This comparison of the

annual variations in rheumatic chorea and rheumatic infection on the whole shows that chorea is the one rheumatic manifestation which best reflects the annual variation of rheumatic infection.

*Recapitulation:* The incidence of chorea is subject to annual variations. Maxima in the frequency of rheumatic chorea are found in 1912, 1921, 1931 and 1938, while minima are found in 1918, 1923, 1936 and 1945. There is also a certain periodicity in the occurrence of rheumatic chorea even though no regular cyclic course can be demonstrated. The interval between two maxima varies between 7 and 10 years, the minima between 5 and 13 years.

The annual variation in the incidence of rheumatic chorea runs parallel with the annual variation for all manifestations of acute rheumatic infection up until 1925, when an increase in the tendency to hospitalization asserts itself for the other rheumatic manifestations. Thus chorea is the one rheumatic manifestation which best reflects the annual variation of rheumatic infection.

#### **Seasonal Variation.**

When it comes to establishing the month for the commencement of chorea in the individual cases, one soon realizes how difficult it is exactly to give the time for the first attack of chorea. Emotional instability, restlessness and moodiness are often present for weeks before the appearance of typical choreic movements. Occasionally the choreic movements may set in so acutely that even the hour for this disturbance can be given precisely, it is true, but in most cases chorea begins gradually and almost unnoticeably. At first, the disturbance of the motility is noticed only when the patient gets tired or is about to make some movements requiring position — *e.g.*, writing or eating. The precise information about the time for the onset of chorea is further rendered difficult through the circumstance that the statement about when the chorea first was noticed as a rule is not given by the patients themselves but by the person taking care of the minor patients.

On going through the case records of the 467 patients in the rheumatic chorea material with regard to the month for the onset of the first attack of chorea, it was found that this could be determined only for 378 patients. The results of this investigation are recorded in Table 18. Also the monthly distribution of the onset in

**Table 18.** *Month of onset of the first attack of rheumatic chorea and cryptogenetic chorea in the cases where the exact month could be established, in Malmöhus county 1910—1944.*

Month of onset	Rheumatic chorea	Cryptogene- tic chorea	Total
January	35	15	50
February	31	16	47
March	35	15	50
April	48	11	59
May	30	21	51
June	23	6	29
July	14	7	21
August	19	12	31
September	21	9	30
October	25	17	42
November	42	10	52
December	55	9	64
Total	378	148	526

the cryptogenetic chorea material was investigated, and it was found to be in keeping with the findings for rheumatic chorea. Therefore, the cryptogenetic chorea material is not dealt with in this section but the results are also entered in Table 18.

The results recorded for rheumatic chorea in Table 18 are presented graphically in Fig. 9, which shows that the onset of chorea occurs in all the months of the year, but most frequently in the months of November—May, with two peaks—in December and in April—while the months of June—October show the lowest incidence of chorea, with a minimum for July, August and September.

In Table 19 the material is divided with reference to the seasons, and Fig. 10 shows the percental distribution of the onset of chorea in the various seasons. This graph shows that rheumatic chorea is a seasonal disease, occurring specially in the winter-spring period.

In the present material on the whole the seasonal variation in the onset of the first attack of rheumatic chorea is in keeping with the statements made in the chorea literature. A similar variation was demonstrated in small materials by Haven (1861), by Koch (1887)



Fig. 9. Month of onset of the first attack of rheumatic chorea (378 cases) in Malmöhus county 1910—1944.

and by Osler (1887), and as early as 1892 it was demonstrated by Lewis, in Philadelphia, in a relatively representative material comprising 717 separate attacks of chorea. Lewis collected his material from the period of 1876—1890 and found a maximal incidence of chorea for the winter-spring season with the highest frequency of onset in March, the lowest in November.

Lewis was also able to show that the seasonal variation in the incidence of chorea largely follows the same rules as in acute rheumatic

Table 19. *Season of onset of the first attack of rheumatic chorea in the cases where the exact month could be established.*

Month of onset	Season of onset	Rheumatic chorea	
		Number	Per cent
March	Spring	113	29.9
April			
May			
June	Summer	56	14.8
July			
August			
September	Autumn	88	23.3
October			
November			
December	Winter	121	32.0
January			
February			
Total		378	

arthritis; for 673 separate attacks of «acute inflammatory rheumatism» he found an increase in the frequency during the winter-spring months with maximum in April, a considerably lower frequency in the summer-autumn months with minimum in September. The same seasonal variation has later been demonstrated by various authors for chorea and other rheumatic manifestations:

Among 144 cases of chorea in London, Poynton *et al.* (1920) found exactly the same seasonal incidence as for 172 cases of «acute rheumatism in children».

Bertram (1925) has reported a material of children from Glasgow in which the seasonal incidence of the first attacks of arthritis (79 cases) ran parallel with that of the first attacks of chorea (35 cases). Both curves show a rise during the autumn, with maximum in November.

From the extensive investigation of «acute rheumatism in children» organized by the London Committee for Child Life Investigation — the results of which are reported in the Medical Research Council Special Reports Series, No. 114, London 1927 — it is evident that the seasonal variation is chiefly the same for «acute rheumatism» as for chorea, although the peak for chorea is found in January and September, for «acute rheumatic fever» in February and November.

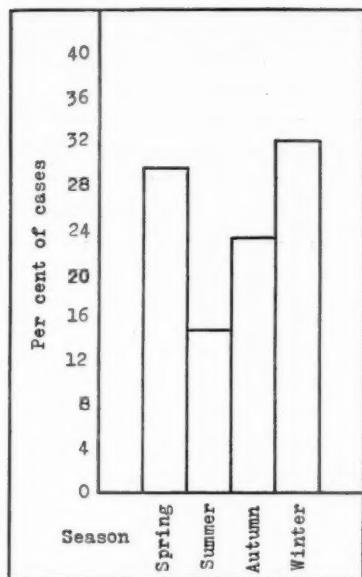


Fig. 10. Seasonal distribution of onset of 378 cases of rheumatic chorea.

Bach *et al.* (1939) studied in London the seasonal incidence among 1500 cases of «juvenile rheumatism», 296 of which were associated with chorea, and found the behavior of chorea in this respect to be concordant with that of other rheumatic manifestations.

Kaiser (1934), studying the factors asserting themselves in rheumatic diseases among 1200 children in Rochester, Minnesota, 360 of whom had chorea, found the seasonal incidence for chorea to be «practically identical with that noted in arthritis». He found the occurrence of the rheumatic diseases to be increased in the latter part of the winter and in the spring.

Jones & Bland (1935) reported from Boston the seasonal variation in the onset of chorea and of rheumatic fever, including recurrences, in 671 cases of chorea and 1209 cases of rheumatic fever. The two curves take the same form with a peak in December—January and another in April.

From Munich, Peters (1939) has reported a statistically established winter-spring peak for 324 cases of «chorea minor». He makes no comparison with any other rheumatic material.

In Sweden, Nordgren (1923), working up a material of children in Stockholm has compared the seasonal distribution for chorea with that for «affectiones rhumatismales» and found the same tendency in the two

Table 20. Month of onset of first attack of rheumatic chorea in Malmöhus county, and month of onset of acute rheumatic infection (arthritis, carditis, chorea, nodules, erythema annulare and tuberculin-negative erythema nodosum) in children in the Pediatric Clinic, Lund, 1910—1944.

Month of onset	Rheumatic chorea		Acute rheumatic infection	
	No.	Per cent	No.	Per cent
January	35	9.3	35	8.0
February	31	8.0	38	8.7
March	35	9.3	39	8.9
April	48	12.7	31	7.0
May	30	7.9	39	8.9
June	23	6.1	29	6.6
July	14	3.7	23	5.3
August	19	5.0	20	4.6
September	21	5.6	44	10.1
October	25	6.6	39	8.9
November	42	11.4	43	9.7
December	55	14.6	57	13.0
Total	378		437	

curves, but the maximum for the incidence of arthritis lies in October, the maximum for chorea in January.

In a material of children from Stockholm, Friedländer (1945) found chorea to be more frequent in the first months of the year, and polyarthritis more frequent in the spring and autumn.

Among 631 cases of «rheumatic fever with chorea minor» among children in Gothenburg, Jacobsson (1946) found the maximum for the incidence of onset in November—January, the minimum in February and in August. Among 112 cases of rheumatic infection in which chorea constituted the initial attack, the onset of chorea was most frequent in January and March.

These chorea materials from various parts of the world are not quite comparable with the present material — not only because of differences in the diagnostic criteria adopted, but also because a geographical factor plays a rôle in the seasonal distribution of the cases. Thus Kaiser (1934) points out that the onset of rheumatic chorea in Rochester, Minnesota, happens preponderantly in the winter and spring, while in England it happens especially in the

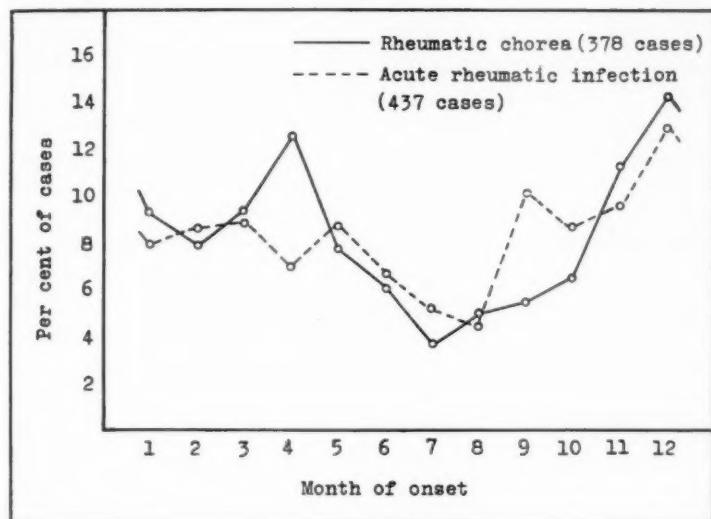


Fig. 11. Graphic presentation of month of onset of rheumatic chorea and acute rheumatic infection as recorded in Table 20.

autumn and spring. Shapiro (1936) has made a comparative study of the seasonal incidence of «childhood rheumatism» in various places (Minnesota, Philadelphia, New York, London, and Scotland), and he emphasizes that the seasonal variation is equal only in the same geographical locations.

In order to obtain a material comparable, diagnostically as well as geographically, to the present chorea material, I therefore investigated all the cases of rheumatic infection, complying with the given criteria, admitted to the Pediatric Clinic in Lund during the period of 1910—1944 with regard to the months of the first onset of a rheumatic manifestation. It has been practicable to establish this date in the 437 cases reported in the two last columns of Table 20.

Fig. 11 gives a graphic presentation of the seasonal variation for the first onset of rheumatic chorea and for that of acute rheumatic infection.

The two seasonal curves have this feature in common that the onset of rheumatic chorea as well as of rheumatic infection on the

whole takes place most often in December. The minima for both curves are found in the summer months — July for rheumatic chorea, August for rheumatic infection. Rheumatic chorea shows a peak in the spring, in April, while the rheumatic infection shows no corresponding peak. This may be expressed in a somewhat generalized form by saying that rheumatic chorea reflects the seasonal variation of acute rheumatic infection in a somewhat exaggerated way.

The seasonal variation has given rise to different interpretations. Lewis (1892) investigated its connection with the atmospheric temperature, moisture and barometric level and found that: »No one element of «weather» explains fully the fluctuations of these tracings for chorea, although in the barometer and storm statistics the relationship appears to be closer than to any other etiological factor or factors that have, as yet, been advanced. The maximum for rheumatic chorea in December and April has been discussed as attributable to forced school work at these times of the year (e.g., Medical Research Council Special Reports Series, No. 114, London 1927).

The connection of chorea with rheumatic infection and, in turn, the connection of the latter with the catarrhal infections — a connection that was realized already in ancient Greece — indicate, however, that, in the first place, it is the epidemiology of the catarrhal infections that forms the seasonal variations in the incidence of chorea. Coburn in 1931 pointed out that the seasonal curve for hemolytic streptococcus pharyngitis takes the same course as the seasonal curve for recrudescences of rheumatism. According to Swift (1947) and Paul (1947), it will nowadays be justified in this respect to express the epidemiological connection between these morbid conditions in a more precise manner as follows: the epidemiology of rheumatic infection is the epidemiology of the hemolytic streptococcus.

*Recapitulation:* The month with the most frequent onset of rheumatic chorea is December, and the next in frequency of onset is April. There is a distinct seasonal variation with most cases in the winter and spring. A comparison with a pediatric material of all rheumatic manifestations shows that the seasonal curve for rheumatic chorea largely follows the seasonal curve for acute rheumatic infection in general.

### Three Special Epidemiological Problems.

There are considerably more epidemiological problems of chorea than touched upon in the preceding. The question about the significance of race, geographical location, dwellings, and many other epidemiological factors to the occurrence of chorea will not be dealt with here as the present material offers no information in this respect. Here merely a brief account will be given of three epidemiological problems that are topical just now, and which our material may throw some light upon.

#### Is rheumatic chorea less common now than before?

The question about a diminution in the frequency of chorea was raised in Sweden by Karlström (1940) and answered by him through investigation of the frequency of chorea minor in all the children's hospitals in Stockholm in 1920—1939. It showed a gradual decrease in the number of cases of chorea in Stockholm, in its absolute number as well as in relation to variations in the censuses. The same question has been dealt with by Jacobsson (1946) in a material of children from Gothenburg in the period of 1922—1940, and he found a reduction in the frequency of chorea after 1933. Every investigation of this kind, however, is rendered considerably more difficult by the annual variation in the incidence of rheumatic infection.

The present material, which represents the urban as well as the rural population in Malmöhus county in 1910—1944 is investigated with reference to the above-mentioned points of view. The material is grouped into three 10-year periods and one 5-year period. The average number of cases per year in each period — of rheumatic chorea (419 cases) as well as of rheumatic chorea+cryptogenetic chorea (599 cases) — is calculated. The resulting figures are then brought in relation to the mean population of 5—19 years, and the number of cases per 100 000 inhabitants is calculated. The findings are recorded in Table 21.

A comparison of the relative incidence of rheumatic chorea and rheumatic chorea+cryptogenetic chorea shows no diminution in their frequencies in Malmöhus county during the first two decades. During the last 15 years, however, the incidence of chorea appears to have decreased somewhat. In principle, then, this result is in keeping with the findings reported from Stockholm and Gothenburg;

Table 21. *Incidence of rheumatic chorea (419 cases) and rheumatic+cryptogenetic chorea (599 cases) in Malmöhus county in the periods of 1910—1919, 1920—1929, 1930—1939 and 1940—1944, calculated per average number of persons aged 5—19 years.*

Period	Average No. of persons of 5—19 years	Rheumatic chorea		Rheumatic chorea+ crypt. chorea	
		Mean per year	Mean per 100 000	Mean per year	Mean per 100 000
1910—1919	137665	13.6	9.9	19.9	14.5
1920—1929	136905	14.6	10.7	20.3	14.8
1930—1939	121944	10.5	8.6	15.2	12.5
1940—1944	109050	6.4	5.9	9.0	8.3

and, furthermore, all the investigations mentioned indicate a reduction in the occurrence of rheumatic chorea during the later years. In estimating the occurrence of chorea, therefore, we have to reckon not only with changes in the composition of the population and with the annual variation in the frequency of rheumatic infection, but also with a decreasing factor in the incidence of chorea.

*Conclusion:* Investigation into the incidence of rheumatic chorea in Malmöhus county in 1910—1944 shows a reduction in the relative frequency of this disease during the last 15 years.

#### Does rheumatic chorea now set in at a younger age than before?

In a paper entitled »Krankheitsdisposition und Entwicklungsbeschleunigung der heutigen Jugend», Bennholdt-Thomsen & Schmidt-Voigt (1940) have employed chorea minor as a test for an »Acceleration der kindlichen Entwicklung» during the last decades. They have looked into the age of the patients at the onset of chorea in Halle 1925—1940 and compared the results to the findings reported by v. Kleist (1907) in a material from the beginning of this century. The first-mentioned investigation comprises 244 cases, the latter 148, in all age classes. On comparison of the two materials, the authors found the typical age for the onset to have shifted from 11 years in the beginning of the century to 8 years in 1925—1940. Further, in the beginning of the century 60.1% of the cases were under 15 years, while in 1925—1940 no less than 84.4% were

under 15. In looking for the cause of this decrease in the age at the onset of chorea, they found it attributable to the increased industrialization and the resulting faster rate of living that has been taking place in Halle in this century.

As our material covers a period of 35 years and comprises the rural as well as the urban population of either sex, it seems of interest with regard to the above topical question to look into the material under these angles, too.

As will be noticed from Table 22 the age at the onset of rheumatic chorea in 1910—1924 is compared with the corresponding age during the period of 1930—1944. Thus, the typical age for the onset of rheumatic chorea in 1910—1924 is found to be 9 years, while for 1930—1944 it is 10 years, and on comparison of the mean ages for the two periods they are respectively 10.1 and 10.6 years. Looking into the age at the onset of rheumatic chorea with regard to urban and rural patients in the two periods, we likewise find no decrease in the age at the onset in the later period. On similar comparison of the material divided after the sex of the patients, neither the male nor the female patients show any decrease in the age at the onset in the period of 1930—1944 as compared to 1910—1924. Thus I have been unable through the present material to confirm the findings reported from Halle.

*Conclusion:* On comparison of our material from 1910—1924 with that from 1930—1944, no reduction in the age of the patients at the onset of rheumatic chorea is found. Nor is there any decrease in the age at the onset when the material is investigated with regard to urban and rural populations and to the sex of the patients.

#### Is the annual variation in the frequency of rheumatic chorea concurrent with that of scarlet fever?

Coburn (1945) states that it has been his experience concerning the epidemiological aspects of rheumatic infection during the last world war, among other things, that the incidence of »rheumatic fever» and that of scarlet fever ran parallel in various places: »Naval activities situated in Northern states have had a relatively high incidence of both diseases, and those in Southern states have had a relatively low incidence of both diseases». Further, in his review of the epidemiological aspects of »rheumatic fever» Paul

Table 22. *Age at the first onset of rheumatic chorea in the periods of 1910—1924 and 1930—1944.*

Age	All cases		Town		Country		Male		Female	
	1910 —24	1930 —44								
2—3	0	0	0	0	0	0	0	0	0	0
3—4	1	0	0	0	1	0	0	0	1	0
4—5	9	2	3	2	6	0	2	1	7	1
5—6	2	3	0	2	2	1	0	1	2	2
6—7	10	13	7	7	3	6	5	4	5	9
7—8	18	9	13	8	5	1	7	4	11	5
8—9	28	16	17	13	11	3	14	7	14	9
9—10	33	13	18	6	15	7	8	6	25	7
10—11	17	21	11	10	6	11	4	6	13	15
11—12	17	17	11	8	6	9	6	3	11	14
12—13	24	10	12	4	12	6	8	3	16	7
13—14	11	8	6	0	5	8	3	6	8	2
14—15	8	8	4	5	4	3	0	2	8	6
15—16	9	1	4	1	5	0	2	1	7	0
16—17	6	4	2	3	4	1	1	2	5	2
17—18	6	2	1	0	5	2	3	0	3	2
18—19	4	2	2	1	2	1	2	0	2	2
19—20	1	3	1	2	0	1	0	1	1	2
20—>	6	4	5	3	1	1	0	2	6	2
	(20, 20)	(20, 20)								
	21, 23	22, 32								
	26, 27)									
Total	210	136	117	75	93	61	65	49	145	87
Mean	10.1	10.6	10.1	10.0	10.7	11.2	9.6	10.3	10.6	10.5

(1947) says that «a good year for haemolytic streptococcal infection is a good year for rheumatic fever».

The hemolytic streptococcus is generally taken to be the uniting link between rheumatic infection and scarlet fever, and the epidemiological aspects of both diseases are ascribed to the epidemiology of the hemolytic streptococcus. How this matter stands has not yet been fully elucidated, but just now this branch of epidemiology is developing fast.

So, on the background of the statements made by Coburn and by Paul it appeared to be of interest to look into the annual distribution

of rheumatic infection as apparent in rheumatic chorea and that of scarlet fever — in order to see whether it might be the same for the two diseases. The present material may contribute to the settling of this question, as it makes it possible to carry out a correct comparison with the frequency of scarlet fever. It is obligatory for Swedish physicians to notify all diagnosed cases of scarlet fever, therefore, it has been possible to obtain reliable data on the annual incidence of scarlet fever in Malmöhus county.

The yearly incidence of rheumatic chorea and scarlet fever for the entire population of Malmöhus county in 1910—1944 is evident from Table 23. A glance at this table shows at once that the annual incidence of rheumatic chorea and that of scarlet fever are not identical; rheumatic chorea shows nothing corresponding, for instance, to the increased incidence of scarlet fever in 1938 and following years. The results of a calculation of the changes in the incidence of rheumatic chorea and scarlet fever in two successive years are reported in Table 24.

In this comparison the difference in the number of cases of scarlet fever between one year and the following year is calculated and when it does not exceed 10% it is recorded as no change (0). When the incidence of scarlet fever shows an increase or decrease over 10% it is recorded as + or -. Then the difference between successive years in the rheumatic chorea material is estimated with regard to increase, decrease or neither, and the coincident changes in the two materials are correlated.

From Table 24 it is evident that an annual change concurrent in the two materials was observed 17 times, no change 3 times and a different change 14 times. The values obtained thus show that, estimated under this angle, there is no regular annual variation in the incidence of rheumatic chorea and scarlet fever.

With reference to the concordance demonstrated before in the annual variation in the incidence of rheumatic infection on the whole and rheumatic infection with chorea, the comparison here carried out between rheumatic chorea and scarlet fever indicates that the annual variation in the frequency of rheumatic infection is not of the same nature as that of scarlet fever.

Here this observation is merely to be mentioned. No discussion of it may be rational until we know more about the significance of the streptococci to the occurrence of scarlet fever and, in particular, rheumatic infection.

Table 23. Distribution after years of rheumatic chorea (first onset) and scarlet fever in the population of the Malmöhus county 1910—1944.

Calendar year at onset	Rheumatic chorea	Scarlet fever	Calendar year at onset	Rheumatic chorea	Scarlet fever
1910	13	664	1928	16	1173
1911	16	1387	1929	16	658
1912	27	1259	1930	17	602
1913	18	1353	1931	19	338
1914	12	1674	1932	11	295
1915	15	2301	1933	12	482
1916	13	1200	1934	8	693
1917	8	719	1935	9	551
1918	5	438	1936	7	409
1919	9	475	1937	7	640
1920	16	653	1938	11	1339
1921	23	512	1939	4	3387
1922	15	907	1940	6	2354
1923	8	560	1941	6	1104
1924	10	366	1942	3	2492
1925	11	279	1943	10	2219
1926	13	197	1944	7	1849
1927	18	464	Total	419	

Table 24. Changes in the incidence of scarlet fever and rheumatic chorea between two successive years 1910—1944 (see the text).

Scarlet fever	Rheumatic chorea			
	+	0	-	
+	6	1	6	13
0	4	0	1	5
-	7	2	7	16
Total	17	3	14	34

*Conclusion:* The present material shows no evidence of any annual concurrent variation in the incidence of rheumatic chorea and scarlet fever.

### 3. Recapitulation.

The epidemiological aspects of chorea are stamped by the epidemiological features of the causes of chorea. As rheumatic infection is the most common cause, it is chiefly this condition that is decisive of the epidemiology of chorea. On the other hand, a study of the epidemiological aspects of chorea gives in some degree a picture of the epidemiology of acute rheumatic infection. In order to get an idea about how chorea stands epidemiologically in relation to rheumatic infection in general, comparative studies are carried out on all the cases of acute rheumatic infection admitted to the Pediatric Clinic in Lund 1910—1944 — a total of 578 children under 15 years.

Looking into the *sex distribution* it is found that the number of boys admitted with rheumatic infection is exactly the same as the number of girls (sex quotient 1:1). In the age group of 0—14 years, however, boys are a little more numerous than girls (1:0.97), and this implies that acute rheumatic infection in Malmöhus county is somewhat more common among girls than boys. On looking into the sex difference in the different rheumatic manifestations, the boys are found to have such manifestations somewhat more often than the girls (1:0.94). The male/female distribution in chorea is 1:1.95, in arthritis 1:0.74, in carditis 1:0.94, and in the skin manifestations 1:1.11. (In our total material of rheumatic chorea it is even 1:2.11). This implies that chorea is the rheumatic manifestation in which the sex difference is greatest.

In materials comprising all age-classes the typical *age for the onset* of acute rheumatic infection is about 9 years. In the present rheumatic chorea material the typical age for all the patients is 9 years, for the boys 8, and for the girls 9 years. The earliest onset for the boys is the age of 4 years, for the girls 3 years, while the highest age at onset for the men is 22 years, for the women 32. Of all the patients with rheumatic chorea 86% had their first attack before the age of 15 years, only 3% at the age of 20 or more. For the male patients the corresponding figures are 89% and 1%, for the females 85% and 4%.

An *annual variation* in the incidence of rheumatic chorea is demonstrable in this material. This periodicity is not regular, the interval between two maxima varying between 7 and 10 years,

while between two minima it varies between 5 and 13 years. The annual variation in the incidence of rheumatic chorea runs parallel with that of all rheumatic manifestations up to 1925, when an increase in the incidence of the other rheumatic manifestations asserts itself — undoubtedly due to a greater tendency to hospitalization. Thus chorea becomes the rheumatic manifestation which best reflects the annual variation of rheumatic infection.

Rheumatic chorea is subject to a *seasonal variation* which largely is identical with that of rheumatic infection in general. In the present material, 30% of the patients became ill in the spring, 15% in the summer, 23% in the autumn, and 32% in the winter. The peak for the incidence of the lesion is found in December — for acute rheumatic infection in general as well as for rheumatic chorea. Rheumatic chorea shows a somewhat lower peak in April, to which rheumatic infection in general has no corresponding feature.

On looking into whether there be any *diminution in the frequency* of rheumatic chorea during the period here investigated, such a feature becomes noticeable in the present material after 1930. This observation is in keeping with similar observations previously reported from Stockholm and Gothenburg.

On investigating whether there be any *reduction in the age at the onset* of rheumatic chorea in the period of 1930—1944 as compared to the period of 1910—1924, no such reduction is found to have taken place — neither in the material as a whole nor on division of the material into urban and rural patients or into male and female patients.

Nowadays it is a prevailing view that the epidemiology of acute rheumatic infection is a part of the epidemiology of the hemolytic streptococcus. Therefore, comparative studies are carried out on the *annual variation in the incidence of rheumatic chorea and scarlet fever*, the outcome of which shows that there has been no concurrent annual variation in the incidence of rheumatic chorea and scarlet fever in Malmöhus county in the period of 1910—1944.

## Summary.

In the course of time the nomenclature of the choreatic disturbance of the motility has been varying, and the import of the term »chorea« has not always been the same. This applies also to »St. Vitus' chorea«, »Sydenham's chorea«, »chorea minor« and other terms. Chorea as well as the other designations are sometimes employed as expressions for a symptom or syndrome, sometimes to designate a disease. In modern time, moreover, there has been a tendency to assign a definite etiological meaning to the terms chorea and chorea minor, which are taken to imply a rheumatic affection. The present chorea nomenclature is somewhat perplexing and difficult to use. Therefore, the primary task of this work has been through studies on the history of chorea and on its etiological and clinical aspects to try to arrive at some guiding principles for a serviceable chorea nomenclature.

The most frequent cause of chorea is found to lie in rheumatic infection. Among the rheumatic manifestations chorea occupies a special position, being the manifestation that is diagnosed most readily, and which leaves the most reliable anamnestic data. Therefore the next task of the present studies has been to give a picture of the epidemiology of rheumatic chorea and in this way also throw some additional light on the epidemiology of the acute rheumatic infection.

The material for the present studies has been gathered from all the hospitals in Malmöhus county where cases of chorea have been treated in the period of 1910—1944. The total material comprises 704 patients in all age classes. Supplementary data concerning these persons have been obtained through questionaries.

In this work »chorea« has been used partly to designate the disturbance of motility and, sometimes, also the choreal syndrome with its disturbance of the motility, decrease in muscular tonus and disturbance of coordination. The term »rheumatic infection« is

here employed to designate the hypothetical *cause* of rheumatic affection. The same term — as well as »acute rheumatic infection» — is used also to designate the *clinical picture* of the affection. The following criteria of rheumatic infection are adopted: arthritis, chorea, carditis, subcutaneous nodules, erythema annulare Leiner, erythema nodosum with tuberculin-negative reaction, and rheumatic granuloma. Chorea is reckoned to be of rheumatic origin when it appears in an individual with some other rheumatic manifestation in his past, present or future history — of course, without any other definite cause of chorea being demonstrable.

A study of the historical development of the *chorea nomenclature* from the Middle Ages to our days leads to the conclusion that the present application of the chorea nomenclature is stamped by perplexity and uncertainty. This is also illustrated very well by the present material — with no less than 17 variations of the diagnosis. Also the systematics employed in the building up of the diagnosis are varying. »Chorea» is employed as the diagnosis for chorea of rheumatic etiology as well as for chorea due to some other established cause — and also for cryptogenetic chorea. »Chorea minor» is employed almost just as often as »chorea», but the former implies a rheumatic etiology more often than does »chorea». In the literature and also in the present material a tendency can be made out that aims at the employment of *etiological systematics* in the building up of the diagnosis in cases of chorea, and this is in keeping with recent medical systematics — and it ought to be practicable. Then the diagnoses »St. Vitus' chorea», »Sydenham's chorea» and »chorea minor» are no longer justified.

A survey of the *causes of chorea* shows that there are many of them. In our material, after the criteria given before, a rheumatic etiology was found in 467 cases, some other established etiology in 22 cases, while in 215 cases the etiology was obscure.

In the discussion of the rheumatic etiology it is pointed out that there is a strong clinical connection between chorea, arthritis, carditis and the other rheumatic manifestations. But the sedimentation rate is often low in chorea (in this material, 0—10 mm. in 45% of the cases recorded), and as long as the pathologic anatomy and bacteriology fail to show any definite connection we have to look upon the etiological connection between chorea and rheumatic infection as a working hypothesis rather than an indisputable fact.

In the section on chorea due to some other demonstrable cause mention is made of prenatal factors (embryonic defect, intrauterine injury, and birth injury to the brain), hereditary degeneration, infection (especially epidemic encephalitis and scarlet fever), intoxication (carbon monoxide, diphtheria toxin), circulatory disturbance (embolism, thrombosis, hemorrhage), disorder of the metabolism, and neoplasms. The material is able only in some degree to illustrate these relatively rare causes.

Under the heading of cryptogenetic chorea various constitutional factors are first discussed as possible causes. It is pointed out that heredity plays a rôle also in the appearance of other forms of chorea besides the one described by Huntington, for in our material chorea is decidedly represented excessively among the parents and sibs of our patients. Mention is made of the great rôle which psychic pressure and trauma have played in the course of time. It is further recorded that 59 out of 245 patients in the questionnaire gave an emotional factor as the cause of their chorea.

The interesting question about the rôle of pregnancy in the appearance of chorea is elucidated — our material includes 18 cases of chorea in pregnancy — and here the author is able to show that pregnancy clearly promotes the appearance of chorea, as in the present material the coincidence of chorea and pregnancy is 3—4 times more frequent than would be expected according to the calculated probability. Unquestionably rheumatic infection was the cause of the chorea in 7 of the 18 cases. Furthermore, as 25 non-pregnant women in the same age group showed a definite rheumatic etiology of the chorea in 6 cases, it may be that rheumatic chorea is more common among pregnant women than among non-pregnant in the same age class. Our material is too small, however, to settle this question decisively. Of the 18 women 6 gave a definite past history of chorea. On follow-up examination of 150 women who had chorea in childhood and all had borne children (315 pregnancies) 9 had recurrence of chorea in connection with pregnancy — and only in one pregnancy. Some authors claim that chorea in pregnancy is a form of toxemia in pregnancy, others assert that chorea in pregnancy often is due to epidemic encephalitis. The latter view is also suggested by the high mortality — higher than for evident rheumatic chorea in pregnancy — but our material cannot contribute any decisive evidence to this effect.

Finally, it is mentioned that most cases of cryptogenetic chorea undoubtedly are due to monosymptomatic rheumatic infection. The subsequently increasing frequency of rheumatic manifestations in the follow-up cases of cryptogenetic chorea speaks in favor of this view. But even though rheumatic infection is the most common cause of chorea, the mere absence of any established etiology does not permit us to take a rheumatic etiology for granted. For some of the other causes of chorea may give the same clinical picture. When the cause of the chorea is known it should be given in the diagnosis; when it is unknown, this should also be evident from the diagnosis.

On looking into the *epidemiology of chorea* the writer is dealing mostly with the epidemiology of rheumatic chorea. In order to correlate chorea with the epidemiology of the acute rheumatic infection, the writer has collated all the first visit cases of acute rheumatic infection admitted to the Pediatric Clinic in Lund in 1910—1944 (578 children), and estimated them after the same diagnostic criteria as employed for the chorea material.

The *sex distribution*, male/female, in this pediatric material is 1:1. But as the sex distribution in the general population for the age class of 0—14 years is 1:0.97, the rheumatic infection becomes somewhat more frequent among girls than among boys. In chorea the male/female quotient is 1:1.95, in arthritis 1:0.74, in carditis 1:0.94, and in the skin manifestations 1:1.11. Thus chorea is the rheumatic manifestation in which the sex difference is most pronounced. In our total material of rheumatic chorea it is even 1:2.11.

In the rheumatic chorea material the typical *age at the first onset* for all the patients is 9 years; for the boys it is 8 years, and for the girls 9 years. The youngest age at the onset is 4 years for the boys, 3 years for the girls; and the highest age at the onset is 22 years for the men, 32 for the women. Of all first onsets of rheumatic chorea 86% take place before the age of 15 years, and only 3% at the age of 20 or later.

An *annual variation* is demonstrable in the incidence of rheumatic chorea, but no regular cyclus. The annual variation in the incidence of rheumatic chorea runs parallel with that of all rheumatic manifestations up until 1925, when an increase in the incidence of the other rheumatic manifestations asserts itself — undoubtedly due to an increased tendency to hospitalization. Chorea is that rheumatic

manifestation which most adequately reflects the annual variation of the rheumatic infection.

A comparison of the annual records of cases of scarlet fever and rheumatic chorea in Malmöhus county 1910—1944 shows no parallelism of annual variation for the two diseases.

Also a *seasonal variation* is demonstrable in the incidence of rheumatic chorea, and this is largely identical with that of rheumatic infection on the whole. In our material, 30% of the patients became ill in the spring, 15% in the summer, 23% in the autumn, and 32% in the winter. The onset was most frequent in December and April.

A *reduction in the incidence* of the lesion is noticeable in our material from about 1930 — an observation that is in harmony with previous observations recorded from Stockholm and Gothenburg.

No *decrease in the age at the onset* of rheumatic chorea can be demonstrated in our material by comparison of the mean age at the onset in the period of 1930—1944 with that in 1910—1924. Nor can any particular difference be demonstrated when the material is investigated with reference to its distribution on towns and country or with reference to the sex distribution.

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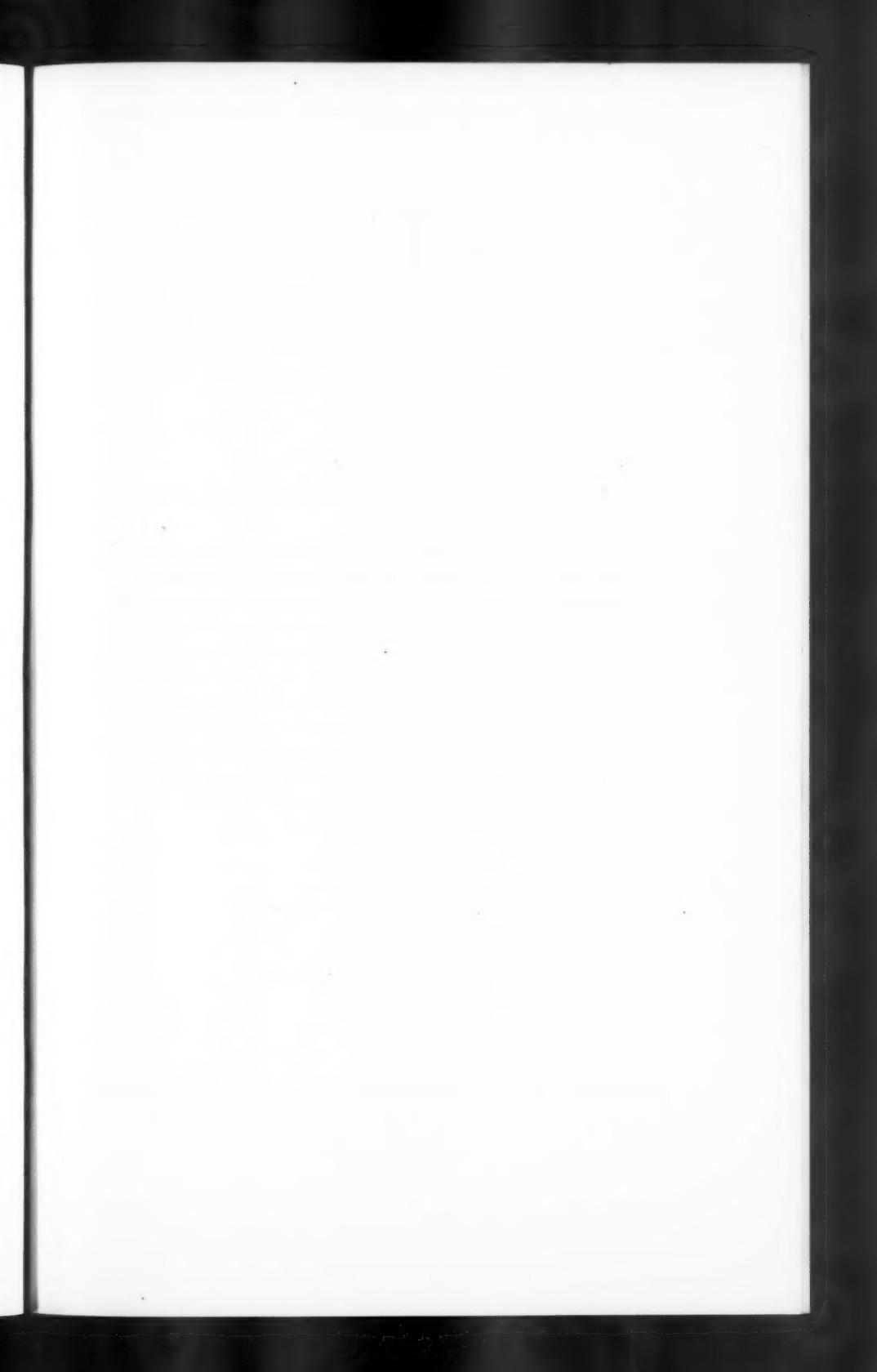
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*Almqvist & Wiksell's Boktryckeri Aktiebolag*  
UPPSALA 1949

# ACTA PÆDIATRICA

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KRONPRINSESSAN LOVISAS BARNSKJUKHUS,  
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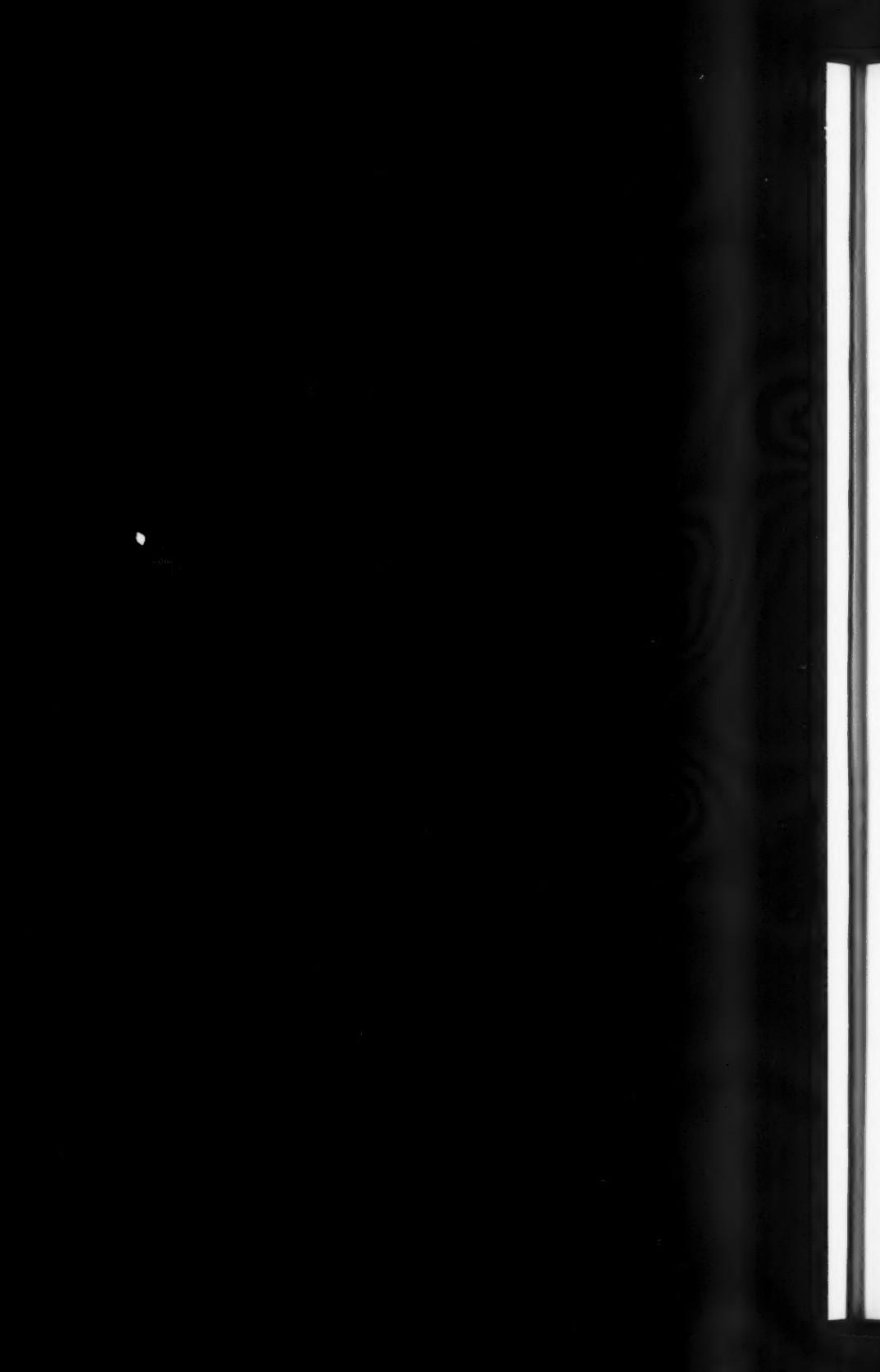
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SUPPLEMENTUM 77

1949

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ACTA PÆDIATRICA SUPPLEMENTUM 77

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THE PROCEEDINGS  
OF THE NINTH NORTHERN  
PEDIATRIC CONGRESS

COPENHAGEN  
AUGUST 13—AUGUST 16, 1948

EDITED BY  
**PAUL DRUCKER**  
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ROSENKILDE AND BAGGER

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## OPENING-ADDRESS

By

CARL FRIDERICHSEN, M. D. (Copenhagen).  
*President of the Congress.*

It is a great honor for me on behalf of the Danish Pediatricians to bid you all a hearty welcome to Copenhagen.

We trust that this Congress may form a valuable link in the chain of preceding congresses and that it may give rise to a profitable exchange of thoughts, constituting thus an incitement to young pediatricians for scientific research — for the good of community and the honor of our Scandinavian countries.

Today it is precisely 29 years ago since Scandinavian pediatricians held their first meeting here in Copenhagen after the first World War. The initiative for that congress was taken by our three honorary members who died all too early:

Professor Monrad, Dr. Loof and Dr. Ernberg.

Unfortunately, the president of the First Scandinavian Pediatric Congress, Professor C. E. Bloch, has not been able to take part in our congress this year. I therefore ask your permission to send Professor Bloch our greetings and at the same time elect him honorary member of the Scandinavian Pediatric Association.

The first time we met here in Copenhagen we were 83 members, and 21 papers were read. Today the members exceed 400 and nearly 100 papers were submitted. This abundance of papers made it necessary, I regret, to reduce the number and limit the speaking time to 10 minutes. We are sorry to have to do this but it seemed essential to gather the whole congress into one section in order to make this meeting the most profitable possible.

Since our last meeting in Helsingfors death has taken its

toll among the members of our association and we have lost the following colleagues:

*Denmark:* Dr. Adolph Meyer; *Norway:* Professor Theodor Frølich, Dr. Ø. Westergaard, Chief School Medical Officer, Bergen, and Dr. Arthur Rød, Oslo; *Sweden:* Dr. Mats Häger, Malmö.

Of these, Dr. *Adolph Meyer* and Professor *Theodor Frølich* were honorary members of the Scandinavian Pediatric Association.

Dr. *Adolph Meyer* died on June 16, 1947, at the age of 75 years, of aleukemic leukosis, that had commenced as an acute thrombopenia. Ten days before his death, Dr. Meyer had apparently been feeling perfectly well, taking part in the discussion at a meeting of the Pediatric Society.

Dr. Meyer was very young when he chose pediatrics for his speciality, and at that time there was only one pediatric clinic in this country. He therefore supplemented his training by a study journey to Vienna and London in 1896-1898, during which, among other things, he commenced his studies on Barlow's disease that resulted in his dissertation for the doctorate of medicine in 1901.

In 1902 he published some detailed accounts of the gastric secretion in infants in the first year of life, in which he demonstrated that barley water was the most serviceable test meal in that age-class to ascertain the acidity of the stomach contents — and this has proved to hold true still.

In 1916-19 Adolph Meyer commenced his studies on whooping-cough which subsequently proved to be of the greatest value to mankind. This work of his made its real headway when he introduced the cough-culture method which has been named after him and is now being used all over the world whenever an early diagnosis of the disease has been necessary. The results arrived at by Adolph Meyer and his collaborators still hold good.

Subsequently he introduced whooping-cough vaccine into this country. These works were presented before the First and Third Northern Congress.

Besides, as secretary general to the Scandinavian Pediatric

Association, Adolph Meyer has been of the greatest significance to the Scandinavian cooperation, gathering and arranging all the details and main features of the first 5 congresses. Personally, Adolph Meyer was of a very modest, almost self-effacing type. His fine and noble trend of thought characterized him throughout life. Through the early diagnosis of whooping-cough and through the prophylactic introduction of the vaccine he has saved the lives of thousands of little children, and it is primarily to his credit that the mortality for this disease — the most murderous of epidemic infections in infancy — in this country has been reduced from 19.2 before 1919 to 2.4 today (per 100.000 inhabitants).

In this association, whose meetings he hardly ever missed, we feel we have lost a very good and very capable colleague at the death of Adolph Meyer.

On this very day, one year ago — on August 14, 1947 — Professor *Theodor Frølich* died, 76 years old, after painful confinement to bed for 5 years.

From 1899 Theodor Frølich served 4 years as Resident Physician to the Pediatric Department of Rikshospitalet, Oslo, during which period he concluded his dissertation, a clinical work on diabetes mellitus in children, based on careful examination of the urine and metabolism, in its thoroughness characteristic of the works subsequently published by Frølich. His investigations on acidosis gave later rise to an interesting and valuable work on the treatment of myositis ossificans with ketogenic diet.

From 1904 to 1908 Frølich was assistant in the Hygienic Institute of the Oslo University. Before accepting this position, he stipulated that he should have an opportunity to work with experimental studies on scurvy in children, Barlow's disease. At that time, the chief of the institute, Professor Axel Holst, was occupied with experimental studies on beri-beri and gradually collaboration was established between these two prominent investigators, both taking an increasing interest in experimental scurvy. The result of this collaboration was the pioneering and now classical work of 1907, with the discovery

of the thermolabile antiscorbutic substance — the subsequently so-called vitamin C — and demonstration of the fact that infantile scurvy (Barlow's disease) is an avitaminosis C.

With our present appreciation of the fundamental significance of these works to all subsequent vitamin research it would only seem reasonable if Frølich had been awarded the Nobel prize for which, indeed, he was nominated. Besides these works, in particular two fields attracted his special interest. He was the first pediatrician in the Scandinavian countries who introduced tuberculin tests on school children with reexamination 10 years later (1912-22). These works were presented before the Fourth and Fifth Scandinavian Congresses.

Another field in which the scientific production of Frølich has left his lasting track was the nutrition of infants. He was the first to introduce the constant addition of cod liver oil and malt to milk mixtures, originally conceived as a specific dietary remedy, and subsequently employed throughout Norway as a normal dietary constituent. This scheme of nutrition has been an important contributory factor in the very low infantile mortality in Norway.

Frølich took the greatest interest in the Scandinavian co-operation, and twice he was president of the Scandinavian congresses.

Personally, Frølich was a very modest man, and what he accomplished he did unobtrusively. He created a particular tone of cosy comradeship in his department, which was stamped by his high ethical view of the medical art and scientific research. He hated German "mastery" and valued the French clinic very highly. It was the bitter irony of fate that this man — the discoverer of the vitamin C — should himself suffer from scurvy under the hard stranglehold of the German occupation.

With the death of Professor Frølich we lost an eminent representative of Scantinavian pediatrics.

Let us honor our deceased members by rising in grateful remembrance of their achievements in our profession.

May their names always be honored in this society.

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Thanks to the fundamental text-book by *Rosén von Rosen-stein*, in Sweden, entitled "Barnsjukdomar och deres botemedel" the thousand-year-old tree of medicine brought forth nearly 200 years ago such a powerful ground shoot that pediatrics now have become a large and independent, rapidly growing tree, spreading its branches and foliage over Community. But the soil has not been equally good for this tree in the different countries. In Sweden today pediatric departments have been established in practically all central hospitals under which also the prophylactic work is taken care of, whereas in Denmark we are still at the prehistoric stage where no pediatric department is attached to any of our large county hospitals outside Greater Copenhagen. The University Clinic of Pediatrics in Aarhus and a private childrens hospital in Odense are the only institutions outside Greater Copenhagen where sick children can be admitted to a pediatric department under an expert pediatrician.

Thus about two-thirds of the children in Denmark are still deprived of expert assistance in this field and yet the development of pediatrics and scientific research have proved very productive in many fields. Here I will mention merely a couple of points that have left their mark also in our programme of papers to be given at this meeting.

The social progress in the form of control stations for infants and babies that were first started and kept up for many years through philanthropic initiative and is now being increasingly elaborated through public support in connection with the assistance of the "health sisters" and welfare nurses. The great value in having these stations managed by expert pediatricians is obvious. In this way, the given instructions concerning the nutrition and development of the children become more uniform and more rational, and the progress made in pediatrics may thus at once become of benefit to the children. The same applies to the schools which in Denmark — outside Copenhagen — are still in need of a pediatric officer.

The increased significance of child psychology and child psychopathy is a point on which psychiatrists and pediatri-

cians have to work hand in hand. It is a field that was broken as early as 1911 by the pediatrician Professor Czerny in his work "Der Arzt als Erzieher der Kindes", and which now has its renaissance in the intensive work now being carried out in various parts of the world. Thus it is the old fields of pediatrics which now are being ploughed again successfully. Furthermore, advances have been made on several points where new technical methods have proved valuable. In this connection it will be appropriate to mention examination with special roentgenography and angiography in congenital heart lesions, and with electro-encephalography in diseases of the brain and convulsive conditions — in both of which fields we have gained new ground for therapeutic possibilities through the collaboration of roentgenologists, surgeons and pediatricians.

In more recent investigations on the salt and water balance it appears as if we have gained better control of the metabolism in acute diarrhea, especially with regard to the significance of potassium and magnesium in the metabolism. The therapy is rapidly making use of the spreading-factor: Hyaluronidase and of radio-active substances for diagnostic purposes. Metabolic studies by means of isotopes still belong to the dim future but the clinical compass needle points definitely towards this new ground still untilled.

The congenital defects have always seemed gloomy to the pediatrician because our therapy here is rather ineffective. But biological studies on the influence of inadequate diet upon the offspring during pregnancy and recent investigations on the significance of infections to the very young fetus have opened new possibilities for restoration of certain congenital malformations which hitherto brought great sorrow to the homes and heavy expenses to the public care of disabled persons. The great advances now being made within physiology, biological chemistry and experimental biology indicate how valuable it will be to the coming pediatric generation to acquire a thorough knowledge of these fundamental aspects of medical science — for the benefit of the future generations.

Ladies and gentlemen!

What I briefly have touched upon makes only a small part of what I should like to point out on this occasion. But time allows me merely to refer to a few features of the more burning questions within our profession. It shows how significant and how essential it is for us physicians with common interests to be able to meet — meet to give and to receive — each being animated by his own special desire to tackle some of the tasks in front of him.

Trusting that our joint meetings and private discussions may have an inciting and beneficial influence on our profession, I now declare the Ninth Northern Pediatric Congress for open.

## MINUTES OF THE PROCEEDINGS

*Saturday, August 14th, 8.30 a.m.*

The president, Dr. C. Friderichsen, opened the Congress.

He proposed as vice-presidents:

Prof. A. Lichtenstein, Stockholm,

Prof. Arvo Ylppö, Helsingfors,

Prof. Leif Salomonsen, Oslo,

Prof. A. Wallgren, Stockholm,

Prof. Preben Plum, Copenhagen.

## SECTION I

*Saturday, August 14th, 9 a.m.—12 a.m.*

Dr. C. FRIDERICHSEN took the chair. The following papers were read:

1. A. LICHTENSTEIN (Sweden): Streptomycin in Miliary Tuberculosis and Tuberculous Meningitis.
2. H. C. A. LASSEN (Denmark): Streptomycin in Generalized Tuberculosis — Preliminary Results.  
Papers 1-2 were discussed by:  
H. ANDERSEN, Denmark.      } Announced Discussion.  
L. SILVERSTOLPE, Sweden.      }  
OLE WASZ-HÖCKERT, JUSTUS STRÖM, G. v. SYDOW, A. WALLGREN, A. LICHTENSTEIN.
3. LEIF SALOMONSEN and MARIT SKATVEDT (Norway): Four Cases of Heredopathia Atactica Polyneuritiformis (Refsum) in Children.  
Discussion by: ERIK GODTFREDSEN, MARIT SKATVEDT.
4. GUNNAR NYHUS (Norway): Congenital Precocious Syphilis Treated with Spirocid in the First Year of Life.
5. HENRIK HAGELSTEN (Norway): Sepsis Neonatorium.  
Discussion by: T. SALMI, KNUD BOJLÉN, A. WALLGREN.

6. GRETA MUHL (Sweden): On Prophylactic and Early Treatment of Infections in Newborn, Especially Premature Children.  
Discussion by: GUNNEL MELIN.
7. BO VAHLQUIST (Sweden): The Rôle of Human Milk in the Transmission of Antibodies.  
Discussion by: B. BROMAN (announced discussion), A. LICHTENSTEIN, P. W. BRÆSTRUP, T. SALMI, B. VAHLQUIST.

## SECTION II

*Saturday, August 14th, 2 p.m.—5 p.m.*

Prof. A. LICHTENSTEIN took the chair. The following papers were read:

8. P. PLUM (Denmark): What is the Attitude of Pediatrics to Psychological Problems of Childhood?
9. SVEND HEINILD (Denmark): Psychosomatic Pediatrics.
10. SIV GUNNARSON (Sweden): Infantile Asthma as a Psychosomatic Disease.  
Papers 8-10 were discussed by: JUSTUS STRÖM, A. WALLGREN, ZAIDA ERIKSSON-LIHR, A. LICHTENSTEIN.
11. C. W. HERLITZ (Sweden): Some Points of View on the Problems of Mental Hygiene in Schools.
12. E. GEDDA (Sweden): Mental Hygiene and Education.  
Papers 11—12 were discussed by: SIV GUNNARSSON.
13. BERTIL SÖDERLING (Sweden): Breast Feeding and Vocational Employment in an Industrial Town. Social-Pediatric Studies.  
Announced discussion: P. NORDENFELT.
14. KARL-AXEL MELIN (Sweden): Electro-Encephalography in Head Injuries in Children.
15. ANDERS THO (Norway): Celiac Disease. Some Experience Achieved from 74 Patients Treated in the Children's Department of Rikshospitalet, Oslo.
16. O. SOMERSALO (Finland): An Attempt to Devise a Glucose Absorption Test.  
Papers 15-16 were discussed by: C. E. RÄIHÄ (announced discussion), B. KROMANN, C. DUEHOLM, E. MANNHEIMER, C. E. RÄIHÄ, A. WALLGREN.

**SECTION III***Sunday, August 15th, 9 a.m.—12 a.m.*

Prof. A. YLPPÖ took the chair. The following papers were read:

17. E. OTILA (Finland): Studies on the Cerebrospinal Fluid in Premature Infants.  
Discussion by: P. PLUM, ARVO YLPPÖ.
18. AINO YLIRUOKANEN (Finland): Sur les Isoagglutinines et les Isolysines chez les Prématurés.  
Discussion by: ARVO YLPPÖ.
19. ARNE ROTHE-MEYER (Denmark): High Protein Nutrition in Prematures.
20. HARALD KREUTZFELDT (Denmark): On Blood-Amino-Acid Levels in Prematures and Infants.
21. ANNALISE DUPONT (Denmark): Investigations on Serum Bicarbonate in Prematures.
22. FOLKE TUDVAD (Denmark): Blood Sugar in Prematures.  
Papers 19—22 were discussed by: J. HENNING MAGNUSSON, P. PLUM, L. SALOMONSEN, LENNART HESSELVIK, A. LICHTENSTEIN, CARL FRIDERICHSEN, BO VAHLQUIST, A. YLPPÖ, A. ROTHE-MEYER, J. HENNING MAGNUSSON, K. KREUTZFELDT, A. DUPONT.
23. BIRGITTA WERNER (Sweden): The Development of Pepsin and Pancreas Proteinase in Premature as Compared with Full-Term Infants.
24. RAGNAR BERFENSTAM (Sweden): Studies on Carbonic Anhydrase in Premature Infants.
25. INGVAR ALM (Sweden): The Early Prognosis for Prematures with Different Forms of Care.  
Discussion by: P. SELANDER, Y. AKERRÉN, C. E. RÄIHÄ, A. YLPPÖ, I. ALM.
26. STIG RANSTRÖM and GERT v. SYDOW (Sweden): Rickets in Premature Infants. A Clinical and Historical Study.  
Discussion by: A. YLPPÖ.

**SECTION IV***Sunday, August 15th, 2 p.m.—5 p.m.*

Prof. LEIF SALOMONSEN took the chair. The following papers were read:

27. E. MANNHEIMER and W. GRAF (Sweden): Heart Tolerance Tests in Children.

28. OLIVER AXÉN and JOHN LIND (Sweden): On the Technique in Angiocardiography on Children.
29. F. ULFSPARRE (Sweden): Angiocardiography in Fallot's Tetrad.
30. JOHN LIND (Sweden): Determination of the Heart Volume on Infants.  
Papers 28—30 were discussed by: E. MANNHEIMER, C. E. RÄIHÄ.
31. AGNER SVENDSEN (Denmark): Investigations on Potassium in Infants.
32. SVEND HEINILD (Denmark) and MAJ LEVANDER LINDGREN: Thrombopenia in Childhood.  
Discussion by: Y. AKERRÉN, L. SALOMONSEN.
33. G. LUNDH (Sweden): On the Occurrence of Massive Aspiration in the Lungs or Obturating Contents in the Trachea and Main Bronchi in Intrauterine and Neonatal Asphyxia.
34. NILS FÜRSTENBERG (Sweden): Asphyxia Neonatorum. Resuscitation by the Supply of Oxygen to the Ventriculus.  
Discussion by: A. YLPPÖ, Y. AKERRÉN, A. WALLGREN, P. KARLBERG, Y. AKERRÉN, Y. ÅKERRÉN, C. E. RÄIHÄ.
35. L. STRÖM (Sweden): A Study of Renal Function with the Aid of Radioactive Phosphorus.
36. JØRGEN VESTERDAL (Denmark): Estimation of Kidney Function in Infancy by Means of Para-Amino-Hippurate Clearance and Inulin Clearance.

#### SECTION V

*Monday, August 16th, 9 a.m.—12 a.m.*

Prof. A. WALLGREN took the chair. The following papers were read:

37. ARVO YLPPÖ (Finland): Treatment of Anaemia with Plasma from Deoxygenated Blood.
38. ARNE NJÅ (Norway): Pernicious Anemia in Childhood.  
Discussion by: BO VAHLQUIST.
39. MARY FALLESEN and ERIK OLSEN (Denmark): Nutritional Experiments with a New Type of Humanized Cow's Milk.

40. OLLE PALMBERG (Finland): On the Water Electrolyte- and Protein Balance in Acute Infantile Dyspepsia.  
Discussion by: P. SELANDER, J. AKERRÉN, BO VAHLQUIST, A. LICHTENSTEIN.
41. AAGE WARMING-LARSEN and E. O. ERREBO-KNUDSEN (Denmark): Peroral Glucose Treatment of Acute Diarrhoea in Infants. I. Ketonemia in Acute Gastro-Enteritis with a Special View to Glucose Treatment.
42. AXEL BIERING (Denmark): II. The Course of Epidemic Diarrhoea in the Newborn under Treatment with Carrot Soup (Idocaron) with and without Addition of Glucose.  
Papers 41—42 were discussed by: ERIK GEDDA, P. SELANDER, P. W. BRÆSTRUP, A. LICHTENSTEIN, N. MALMBERG, ERIK FRISELL, V. RANTASALO, AAGE WARMING-LARSEN, AXEL BIERING.
43. P. KARLBERG (Sweden): Experiences with a Simple Clinical Method for Determination of the Metabolism in Infants.  
Discussion by: ERIK MALM, C. E. RÄIHÄ.
44. HANS-OLOF MOSSBERG (Sweden): The Prognosis in Obesity in Children.
45. K. BIERING-SØRENSEN (Denmark): Basal Metabolism in Obese Children.  
Discussion by: HANS-OLOF MOSSBERG.
46. JØRGEN PEDERSEN (Denmark): The Blood Sugar Level under Standard Conditions During the First Day of Life in Children of Diabetic and Normal Mothers.  
Discussion by: JØRGEN PEDERSEN.
47. JØRGEN PEDERSEN and ANNIE SCHONDEL (Denmark): Follow-Up Examination of Children of Diabetic Mothers.  
Papers 46-47 were discussed by: A. LICHTENSTEIN.

## SECTION VI

*Monday, August 16th, 2 p.m.—5 p.m.*

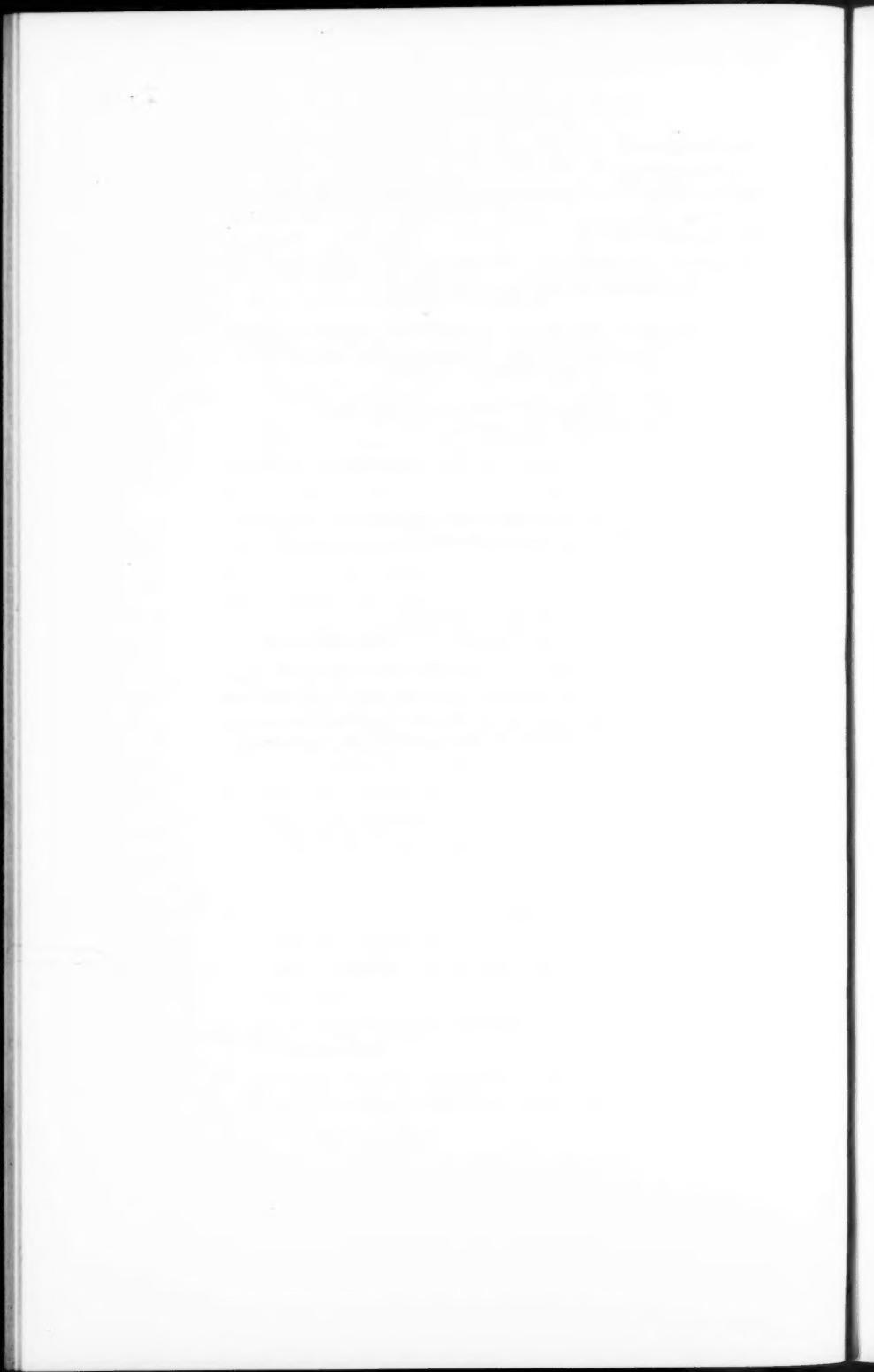
Prof. PREBEN PLUM took the chair. The following papers were read:

48. VILJO RANTASALO (Finland): A Diphtheric Milk Epidemic in Helsingfors.
49. GUNNEL MELIN (Sweden): Some Bacteriological Points of View Concerning Infections of the Upper Respiratory Passages in Infants.

50. P. W. BRÆSTRUP (Denmark): Acute Obturative Laryngo-Tracheobronchitis.  
Papers 49-50 were discussed by: LENNART HESSELVIK (announced discussion), ERIK FRISELL, BERTIL SÖDERLING, GUNNEL MELIN.
51. K. BIERING-SØRENSEN and J. DRAGSTED (Denmark): Peroral Administration of Penicillin to Infants.
52. TORBEN JERSILD (Denmark): Comparative Effects of Intermittent and Continous Penicillin Therapy (Procaine Penicillin).  
Discussion by: P. KARLBERG, T. SALMI.
53. AAGE VIDEBÆK (Denmark): Cancer in Childhood.  
Discussion by: MATTI SULAMAA.
54. MATTI SULAMAA (Finland): On the Mortality in Infantile Surgery and its Causes.
55. STIG NORSTEDT and LENNART SILVERSTOLPE (Sweden): A Simplified Quantitative Method for the Examination of Urine Sediment.
56. ZAIDA ERIKSSON-LIHR (Finland): How to Organize the Treatment of Allergic Diseases in Children.  
Discussion by: SVEN KRAEPELIN, A. LICHTENSTEIN.
57. HILMA ALAROTU (Finland) and ERNA CHRISTENSEN (Denmark): Studies on Changes in the Sympathetic Ganglia of the Pyloric Portion of the Stomach in Infants with Pylorospasms.  
Discussion by: C. E. RÄIHÄ, A. WALLGREN, C. E. RÄIHÄ.

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Congressional Exhibition.



## **SECTION I**

**SATURDAY, AUGUST 14.**

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*From the Pediatric Clinic at Kronprinsessan Lovisa's Children's Hospital, Stockholm.  
Head: Professor A. Lichtenstein.*

## STREPTOMYCIN IN MILIARY TUBERCULOSIS AND TUBERCULOUS MENINGITIS

By  
**A. LICHTENSTEIN (Sweden).**  
*Author's abstract.*

Reports in the literature concerning about 1000 cases of tuberculous meningitis show that the life of the patient was saved in about 30-40 %, of which, however, only about one-third — i. e., 10-15 % at the most — may be designated as cured or practically cured. Considering that the observation period often has been too short — at least one year is required — these figures are maximum figures. The risk of a late relapse has to be reckoned with. In miliary tuberculosis without meningitis the results are better, but secondary meningitis appears not infrequently.

In Sweden so far 60 odd cases of meningitis have been treated with streptomycin, and of these merely 24 have been observed sufficiently long. Only 5 of these patients are living in a satisfactory condition, though all present vestibular damage. 14 have died, and in 4 the result is defective recovery or chronic illness (information about one patient is wanting). Not infrequently does streptomycin give rise to subchronic tuberculous meningitis. For given in therapeutic doses the remedy has mainly a bacteriostatic, not bactericidal, effect on the tubercle bacilli. In certain cases tubercle bacilli are found in the cerebral spinal fluid as well as recent tubercles in the meninges after up to 1 year of intensive treatment.

Our knowledge is still incomplete as to the mechanism of the action of streptomycin *in vivo*, and of its absorption, distribution and excretion, also with regard to the best way of administration, e. g., about the necessity of intralumbar injec-

tions, and about the optimal dosage. The necessity of the remedy makes a cautious dosage essential, but small doses may increase the risk of resistance. At present I give 100 mg. 4-6 times daily intramuscularly and 25-50 mg. intralumbally, at first once a day, then every 2 or 3 days, in periods of 3 weeks for at least 3-4 months. Smaller doses seem desirable.

Possible intracerebral "foci" are but slightly accessible for treatment.

Certain experiences suggest that a combination of streptomycin with some sulfonamide preparation may improve the therapeutic results.

On account of the uncertain effect of streptomycin and its toxicity — in one of my cases an irreversible vestibular injury appeared already after 6.5 g. — it is desirable to obtain a new atoxic remedy with not only bacteriostatic but also bactericidal effect.

From the Blegdam Hospital, Epidemic Department, Copenhagen.  
Head: Professor H. C. A. Lassen.

## STREPTOMYCIN IN GENERALIZED TUBERCULOSIS PRELIMINARY RESULTS

By  
H. C. A. LASSEN (Denmark).  
*Author's abstract.*

In the Blegdam Hospital, since June 1947, we have treated altogether 25 patients suffering from tuberculous meningitis with or without miliary tuberculosis of the lungs and five patients with miliary changes in the lungs without tuberculous meningitis. At first we gave the children about 100 mg. per kg. daily intramuscularly, later 50 mg. per kg., distributed on two-four daily injections. Adults were given 1 gram three times or 1 gram twice daily. As the passage of streptomycin from the blood to the spinal fluid appeared not have been investigated sufficiently, Professor K. A. Jensen and I began to look into the passage of this antibiotic from the blood stream into the spinal fluid after intramuscular injections. All our patients with one exception have been treated with intramuscular injections alone. In these studies the streptomycin concentration in the blood was found to keep so well that it may be considered sufficient to give two—at the most three—intramuscular injections a day. While only an insignificant amount of streptomycin passes over into the spinal fluid in patients with intact meninges, a considerable amount passes over into the spinal fluid in cases of purulent meningitis or tuberculous meningitis. In nearly all the cases the values obtained in the spinal fluid were 20-50 times higher than the in vitro sensitivity of the bacillary strains found in the spinal fluid of the patients.

A typical experiment is shown in Fig. 1.

From numerous concordant experiments we have arrived

## Section I

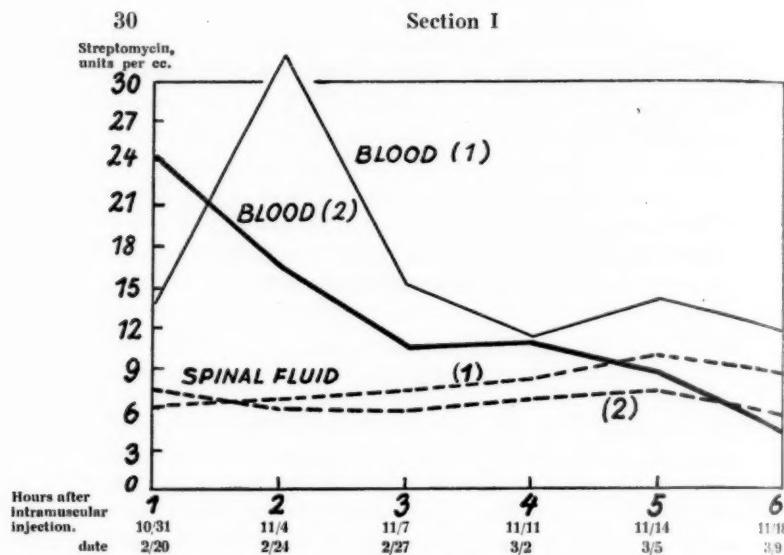


Fig. 1.

E. A., five years, tuberculous meningitis. Earliest symptoms noticed September 26, 1947, admitted to the Blegdam Hospital September 30, died May 15, 1948.

Dosage of streptomycin: 500 milligrams intramuscularly four times daily, corresponding to about 100 milligrams per kilogram body weight per day. The series marked (1) was started after the disease had lasted five to six weeks, the other series after five months. The strain of tubercle bacilli, a human type, found in the patient's spinal fluid was very sensitive to streptomycin. One eighth of one unit of the antibiotic was sufficient totally to inhibit growth of this strain.

at the conclusion for the time being to treat patients with tuberculous meningitis exclusively with intramuscular injections. The therapeutic results for 26 patients who were treated for more than four months will be given briefly. My estimation of these preliminary results, I think, has been very critical.

*Of 15 patients with tuberculous meningitis without miliary tuberculosis of the lungs three are now "well". At this writing (Jan. 11, 1949), in these three cases respectively 19, 18 and 17*

months have passed since the onset of illness, and 14, 11 and 10 months since the discontinuance of treatment. Of the remaining 12 patients three are living—13-10 and seven months respectively after the commencement of treatment. Of these three patients, two are in good shape but unquestionably the prognosis is dubious, while in one the condition has turned into a chronic cachectic-encephalitic state which undoubtedly will terminate fatally before long. Five patients have already died in a similar state after half-one year of treatment, and four died early without any effect from the treatment. Thus the treatment showed effect in 11 out of 15 cases.

Our six patients with tuberculous meningitis as well as miliary tuberculosis in the lungs have fared worse than the 15 with tuberculous meningitis alone. Four died quietly without any effect from the treatment, whereas two patients — nine months and three years old — improved promisingly for a long time. The one year old boy died rather suddenly in a relapse after seven months medication and recently the three years old girl has shown signs of relapse only a few days after streptomycin was discontinued after more than seven months continuous therapy. Her ultimate prognosis is bad, I fear.

Finally, we have had five patients with miliary tuberculosis of the lungs without tuberculous meningitis. Here the results are encouraging, as only one patient died, while two have been discharged with normal roentgenograms and in good general condition, one appears to be on the road to recovery and one has had a meningitic relapse. In the last-mentioned case the treatment was started on May 27, 1948, and the patient responded very favourably. In the latter part of July the changes in the lungs had disappeared almost completely, therefore it was decided to make a pause in the treatment. A few days later, after the discontinuance of streptomycin, the patient had a headache and started to vomit, and now the spinal fluid was found to show changes typical of tuberculous meningitis. In spite of renewed treatment this patient died Nov. 10, 1948.

Thus the preliminary results obtained with intramuscular

injection of streptomycin have been fairly encouraging even though considerable reservation is essential in judging the final outcome.

Of complications we have seen but few, moderate eosinophilia, drug fever once, never local discomfort of any significance. On the other hand, in all the cases examined, the vestibular function has been destroyed within one-three months after the commencement of the treatment. Microscopic examination has shown degeneration and inflammatory changes in the central representation of the vestibular nerve, and also peripheral inflammatory changes in the spiral ganglion of the cochlea and in the vestibular cochlear nerves in the internal auditory meatus.

#### DISCUSSION

*Henning Andersen (Denmark).*

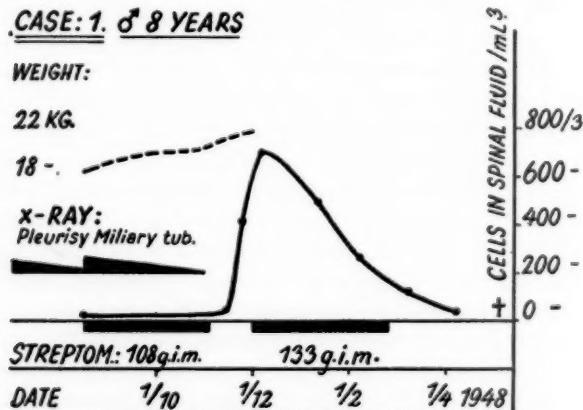
In the Fuglebakken Children's Hospital 3 cases of tuberculous meningitis have been treated with streptomycin, namely:

CASE 1. ♂ 8 YEARS

WEIGHT:

22 KG.

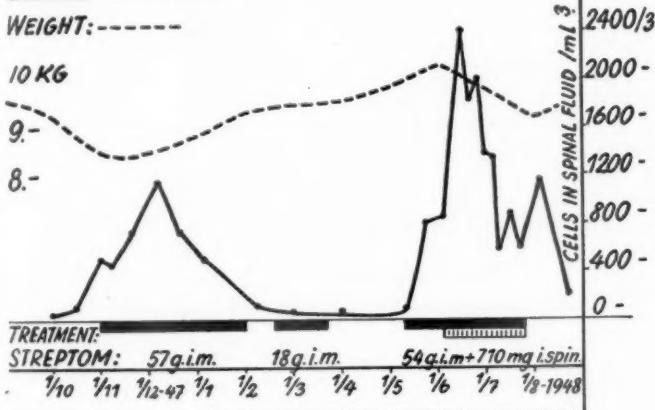
X-RAY:  
Pleurisy Miliary tub.



*Case 1.* Boy, 8 years old. In the course of tuberculous pleurisy there was a miliary dissemination in both lungs. He was treated with altogether 108 g. streptomycin given intramuscularly in about 2½ months, after which the changes in the lungs disappeared

completely and his condition was so good that he was assumed to have become well. About 3 weeks after the discontinuance of the streptomycin therapy, however, tuberculous meningitis developed and in spite of treatment with 133 g. streptomycin in 5 months, under which the spinal fluid became normal, he died about 6 months after the onset of the meningitis in a state of cachexia with encephalitic features. Autopsy showed extensive tuberculous processes on the surface of and in the brain; and cultures as well as smears from the brain tissue showed + TB.

CASE 2., ♂ 2 YEARS



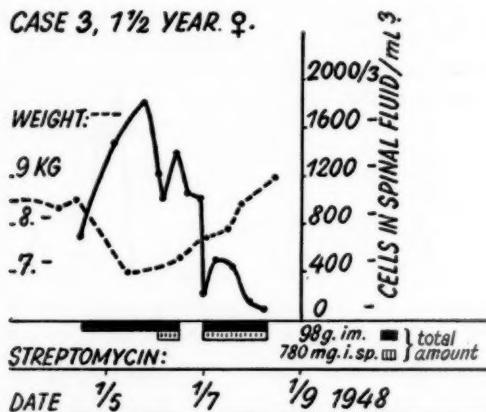
Case 2. Boy, 2 years old, with tuberculous meningitis. Through 4 months he was given altogether 72 g. streptomycin intramuscularly, after which the spinal fluid was normal, the weight increasing, and the general condition excellent. Two months later a relapse appeared for which he was treated through 3 months with altogether 54 g. streptomycin intramuscularly and 710 mg. intraspinally in about 1 month. After this the cell count is approximately normal and the general condition fairly good. The child is playing naturally in bed, and the weight has commenced to increase.

Case 3. Girl, 18 months old, who is treated for tuberculous meningitis with altogether 54 + 44 g. streptomycin intramuscularly and 780 mg. intraspinally through about four months with an intervening pause of 2 weeks. After this fall in the spinal fluid cell count to nearly normal, good increase in weight, and excellent general condition.

None of these patients has shown symptoms of visual or auditory impairment, or disturbances in the hemopoietic system.

In Cases 2 and 3, in which streptomycin was also given intraspinally (30 mg. in 0.6 cc. saline), the injection was followed immediately by a rise in the cell count. A similar increase, which has to be looked upon as signifying a state of irritation produced by streptomycin has been found also in a child with an inoperable tumor, but with normal spinal fluid, after intraspinal injection of streptomycin.

### CASE 3, 1½ YEAR. ♀.



*Lennart Silverstolpe (Sweden).*

*Significance of the demonstration of tubercle bacilli in the cerebrospinal fluid with a new method also under treatment with streptomycin.*

In the Norrtull Hospital in Stockholm, for some length of time we have been performing continuous examinations for the presence of tubercle bacilli in the cerebrospinal fluid from our patients with tuberculous meningitis under treatment with streptomycin. For this we have employed a method elaborated by us that takes into account the low specific gravity, and with which we have been able in most cases to make the diagnosis early and institute streptomycin therapy immediately after.

*Fig. 1.* The material comprises 19 cases of guinea-pig positive tuberculous meningitis, 18 of which were treated with streptomycin. Six patients died. Of the total 19 cases 6 were treated in the Norrtull Hospital; from the remaining cases, specimens were sent

19 Cases of Tuberculous meningitis (guinea-pig positive).Treated with streptomycin.

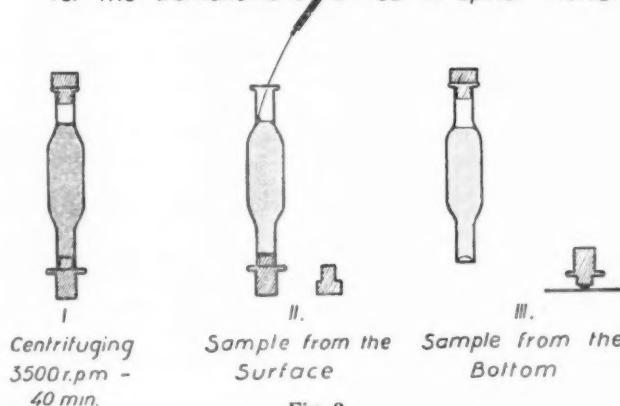
Norrstull Hospital .....	6
Stockholm Epidemic Hosp. ....	7
Vänersborg .....	3
Karlstad .....	1
Bäckefors .....	1
Uttran .....	1
12 Löwenstein pos. ....	63,2 %
10 Dubos pos. ....	52,6 »
18 Direct smears (Acid-fast rods) ....	94,7 »

Fig. 1.

to us from other hospitals where the patients were under treatment, and thus we have been able in our tuberculosis laboratory to follow these cases. I wish here to thank the chief physicians concerned for their kindness in placing the cases at our disposal.

In cultures on Löwenstein's medium we have found growth of tubercle bacilli in 12 cases (= 63.2 %); 10 have yielded growth on Dubos' medium (= 52.6 %). The striking feature is that in 18 of the 19 guinea-pig positive cases we have been able to demonstrate acid-fast rods in direct smears (= 94.7 %).

Fig. 2. It will be convenient to demonstrate the technique briefly

TECHNICfor the Demonstration of Tbb in Spinal Fluids

Centrifuging  
3500 r.p.m. -  
40 min.

Sample from the Surface      Sample from the Bottom

Fig. 2.

## 19 Cases of Tuberculous Meningitis

### Surface and Bottom Distribution of Tbb before Streptomycin Treatment

	18 Direct smear	12 Culture (Loew)	19 Guinea-pig
— Surface pos. only	<b>8 = 44.4%</b>	<b>2 = 16.7 %</b>	<b>3 = 15.8 %</b>
— Surface and Bottom	<b>6 = 33.4%</b>	<b>8 = 66.6%</b>	<b>15 = 78.9 %</b>
— Bottom pos. only	<b>4 = 22.2%</b>	<b>2 = 16.7 %</b>	<b>1 = 5.3 %</b>

Fig. 3.

as follows: *Step I*: The spinal fluid is withdrawn directly into the biconical centrifuge tube\*), which holds 8 ml. If the tube is not filled, saline is added up to the mark. The tube is centrifuged at a rate of 3500 revolutions per min. for 40 min. in a centrifuge with cardanic suspension\*\*) of the tubes. *Step II*: shows the technique of taking a sample from the surface, by means of a platinum loop from the periphery of the surface where the lighter bacteria are obtainable on account of the menicus form of the surface fluid. — *Step III*: shows the technique of taking a sample from the bottom. While the upper stopper is left in place the bottom stopper is taken out, and a smear is made on the slide with the stopper itself. All the rest of the fluid remains in the tube without running out.

This method has proved to give an increased yield of positive tests, not only because the surface layer is examined but also because the bottom technique is improved.

*Fig. 3* illustrates the distribution of the tubercle bacilli between the surface and the bottom in the tube. From this tabulation it is evident that in 44.4 % of the smears, in 16.7 % of the cultures, and in 15.8 % of the guinea-pig tests the acid-fast bacilli were found only on the surface in the tube. So, with the technique usually employed, these cases would have been missed.

*Fig. 4* shows a couple of cases from the Norrtull Hospital, of

\*) Fabricated by Rudolph Grave, Stockholm.

\*\*) Fabricated by Kifa, Stockholm.

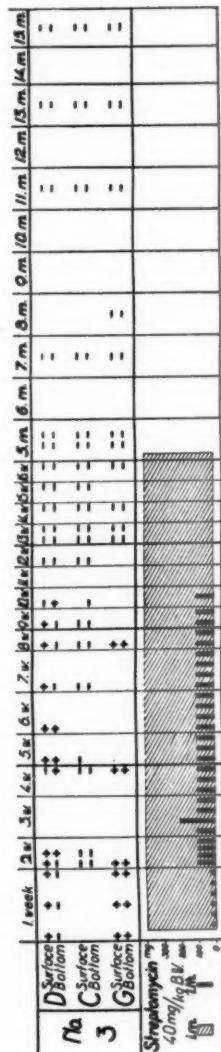
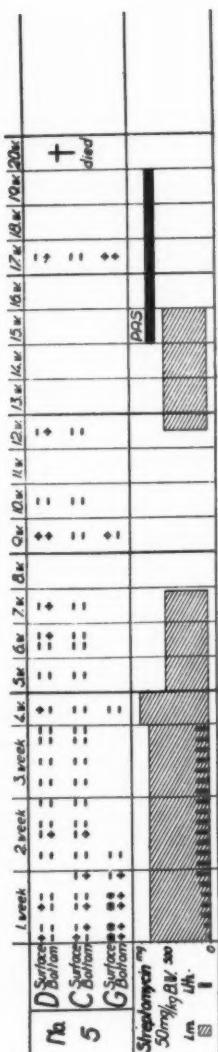


Fig. 4.

which one was followed for 5 months, the other for 15 months with direct smears (D), cultivation (C), and inoculation of guinea-pigs (G). — The upper case is that of a girl, 4 years old. It will be noticed that the examination turns out positive only from the surface in the direct smear and on cultivation, and that the guinea-pig test is much more strongly positive from the surface than from the bottom. On the same day as acid-fast rods were demonstrated in smears, treatment with streptomycin was instituted intramuscularly (hatched curve) as well as intrathecally (stocks). During the second week of treatment the bacilli are found in the bottom layer, which we usually interpret as a bacteriostatic effect, and in the third week all the tests are negative. In the second and third months bacilli are again found in a few tests, and even on the surface, which is a poor sign, and the patient died in the fifth month.

The other case is that of a girl, 3 years old, in whom as far as we now are able to estimate, streptomycin therapy has been more effective. As in the first case, at first tubercle bacilli were demonstrated only in the surface layer, which, as mentioned before, indicates young virulent bacilli. In the second week tubercle bacilli were demonstrated also in the bottom layer. Acid-fast rods were demonstrated even in the third month. Since then, however, all the tests have been negative — direct smears as well as culture and inoculation of guinea-pigs — and now we have followed the patient up to the 15th month.

*Fig. 5.* The following 2 cases are from the Epidemic Hospital. In the upper case the first specimen gives a positive result only from the surface both in cultures, guinea-pigs, and direct smears. After the institution of streptomycin treatment tubercle bacilli are obtained mostly from the bottom layer in this case, too. Negative smears in the 11th to the 16th week are accompanied by negative guinea-pig tests. After this, however, acid-fast bacilli are found in smears also from the surface, which is an omen of increased activity of the tubercle bacilli. Indeed, this could be confirmed through positive outcome of guinea-pig tests. In the sixth week acid-fast rods were also found in smears, but without the guinea-pig test becoming positive, which should be interpretable as avirulent tubercle bacilli, impaired or killed by streptomycin. The bacilli have been found again in the 17th week. Streptomycin intrathecally was put in but in spite of that the patient died in the 7th month. The *lower* table illustrates an other case.

The cases demonstrated here illustrate very well the support offered by this method in the diagnosis and treatment of tuberculous meningitis.

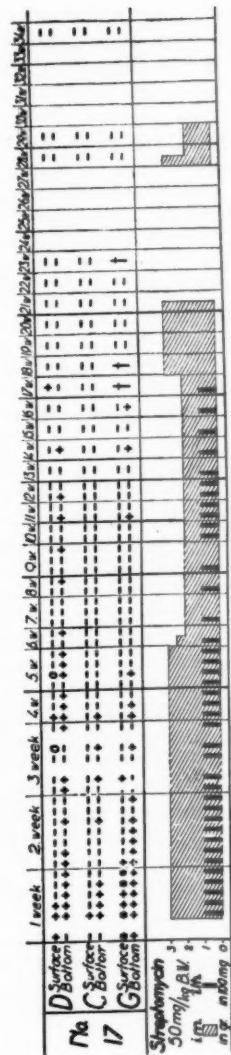
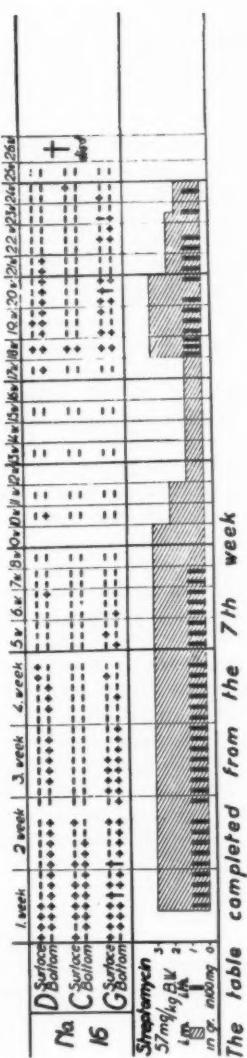


Fig. 5.

Ole Wasz-Höckert (Finland).

In the Children's Hospital in Helsingfors we have had occasion to treat 39 tuberculous children with streptomycin. Of this total 17 were suffering from tuberculous meningitis, 11 from miliary tuberculosis.

The age of the 17 meningitic patients varied from 4½ months to 12 years, with an accumulation of cases at the age of 6 months to 3 years. In spite of intramuscular and intrathecal administration of streptomycin, 13 patients died. No agonal cases were treated, but 3 cases of very advanced meningitis were under treatment one week without any favorable effect. In two cases the meningitis appeared suddenly although the patients had been treated already for miliary tuberculosis with streptomycin through three months. The access to streptomycin has been somewhat decisive of the dosage, which has varied between 20-40-60 mg. per kg. of body weight and day (thus, for instance, a child of 10 kg. was given 50 mg. 8 times daily). The intralumbar and intraoccipital doses were lower: 10-20 mg. per day, given at once; in a few cases 50 mg. With this treatment it was possible to maintain life for about 3 months. In one case the patient, a girl of 2 years, was blind at the discharge (optic atrophy) but otherwise in good condition after 5 months of treatment; 3 months later she had a relapse and died in spite of treatment with streptomycin for one month.

Four cases (1½-7 years) have given reasons for good expectations as to the future. The diagnosis was unquestionable. The patients were treated through 4-9 months. The observation period is 4-6 months. One patient who had been treated for 7 months, had a relapse 2 months later, but is now improving again; still, the prognosis is somewhat dubious (spinal fluid cell count 40 to 60). In this group there has been no untoward effect — apart from "petit mal" in a child of 7 years (total dose: 45 g. streptomycin, ½ g. of this given intralumbarly).

In our hospital it has been necessary to adopt the principle, if necessary, to omit streptomycin therapy in cases of meningitis in favor of cases of miliary tuberculosis and slighter degrees of primary tuberculosis in infancy.

11 patients were suffering from miliary tuberculosis, which in 4 cases terminated fatally in spite of 4 weeks treatment with streptomycin. These patients were from 5 months to 2 years old, and the dosis was 40-50 mg. per day/kg. The youngest patient had a rather severe gastro-enteritis, which compromised the therapeutic result.

Of the remaining 7 patients 4 were discharged after 3 to 8 months' treatment with a dosage of 25 mg. per day/kg. in 3 cases, 60 mg. in one (5 months). In all these cases, roentgenography

showed distinct clearing of the lungs. Clinically there was a good tendency to healing and gaining in weight. The total dose was 15, 16, 19, and 64 g. respectively. There were no untoward effects from the streptomycin therapy.

Three patients are still under treatment which in 2 of the cases has now lasted 4 months, in the third case over 2 months. They show a tendency to healing, but with these doses we generally have seen a noticeable clinical and roentgenological improvement when the treatment has been given for at least 3 months. In the cases now under treatment the dosis is 25 to 30 per day/kg. No neurological by-effects. In one case miliary processes in the eye ground have shown distinct regression.

*Justus Ström (Sweden).*

In connection with Dr. Silverstolpe's communication about direct demonstration of tubercle bacilli in the cerebrospinal fluid in cases of tuberculous meningitis, I wish to emphasize that I think this means a great advance. In our 7 cases of tuberculous meningitis, in the Epidemic Hospital of Stockholm, 5 of whom are living, we found, however, that intrathecal administration of streptomycin is not practicable until abacillarity has appeared. One will have to be content to obtain that the regular bacillarity disappears. At any rate we shall then have a little more solid ground to stand on when it comes to outline the therapy.

Of course here we are not only to consider the abacillarity but also the regression of the changes in the spinal fluid and the clinical course — as is obvious in such a disease. It may be, however, that the occurrence of tubercle bacilli in the spinal fluid and the rapidity with which they disappear again may be of help to us, when the question is to decide whether we are able to decrease the dosage and the intrathecal administration, and perhaps going to employ intramuscular administration alone — as suggested by Professor Lassen.

*G. v. Sydow (Sweden).*

With reference to Professor Lichtenstein's lecture I should like to give an account of a case I have treated because here we decidedly have the impression of the streptomycin therapy not becoming really effective till it was combined with *heparin therapy*.

This is the case of a boy, 3½ years old, who was admitted on March 5 1948 with a typical history: Onset of headache about one week before, increasing lassitude and indolence. There was no distinct rigidity of the neck on admission, but the findings in

the spinal fluid were typical, including growth of tubercle bacilli of human type in cultures.

Streptomycin treatment was instituted at once in the dose recommended, among others, by Lichtenstein: 0.1 g. five times daily intramuscularly and 0.3 g. intrathecally daily. This was effective insofar as cultures from the spinal fluid every 2 weeks no more showed tubercle bacilli, but the general condition was getting worse and worse: the rigidity increased and the patient became soporose, completely remote, saying nothing, and failing to react when addressed. After 3 weeks, therefore, the streptomycin dose was doubled, intramuscular as well as intrathecal, without any other noticeable effect than a slow fall in the temperature to a sub-febrile level. The general condition was still getting worse and worse.

Then the idea of using the heparin therapy occurred to me. I imagined that perhaps thick coats of fibrin round the tuberculous foci might prevent the streptomycin from reaching these, or that they at any rate inhibited clinical improvement. From April 12 — that is 5 weeks after admission — the patient therefore was given 5 mg. heparin a day intrathecally. We tried to give it intravenously, too, but had to give it up for technical reasons. — From the commencement of the heparin treatment we found a striking improvement of the general condition of the boy. He commenced talking again, at first single words, then more, and from the middle of May he talked quite easily and answered adequately when addressed. Now he also commenced moving spontaneously, sitting up in bed and so on, and from the middle of June — 3 months after the onset of illness — he behaves quite like a child of four, being difficult to keep in bed, talking and playing with his comrades. Clinically there is still a moderate increase in cells in the spinal fluid and a high sedimentation rate, but otherwise quite normal findings.

The change in the course of the case from the very commencement of the heparin treatment was so striking that I found it worth mentioning even though it involves merely a single observation.

#### A. Wallgren (Sweden).

The greatest importance to the prognosis of streptomycin-treated tuberculous meningitis and miliary tuberculosis is attached partly to the age of the child, partly to the point of time of the institution of treatment. The British collective investigation under the management of the Medical Research Council shows, as was to be expected that the prognosis was much worse for children under 3 years. In Belfast, for instance, this has led to children in this age-class not being treated, which may perhaps be justified if the access to

streptomycin is extraordinarily slight. There are a number of cases of tuberculous meningitis, however, that have healed under streptomycin treatment even though these patients belong to the youngest age-class.

As to the juncture for the institution of treatment, of course, it is ideal to begin the treatment before the meningitis becomes manifest. On account of the toxicity of the remedy, then, prophylactic treatment should be employed only in such cases of primary tuberculosis where the risk of meningitis and miliary tuberculosis is particularly great — i. e., in infants within the first 3 months after the manifestation of the tuberculosis.

In infants we have to reckon that 30-40 % of all those infected with tubercle bacilli will get tuberculous meningitis or miliary tuberculosis. In Norrtull Hospital we have treated 5 cases of tuberculosis in infants as mentioned with 50 mg. per day/kg. So far, no child has become ill with meningitis and in no case has any toxic effect been noticed.

Many questions are still waiting to be answered regarding the streptomycin therapy. When is the intraspinal treatment to be discontinued? When may we discharge the patients? How are the aftertreatment and follow-up examination to be managed? Are we to give streptomycin intraspinally too, or is it just as effective, as stated by Professor Lassen, to give it only intramuscularly, which, among others, the collective investigation of the Medical Research Council has found insufficient? Indeed, we see not infrequently that miliary tuberculosis, under streptomycin treatment goes on to meningitis, which does not improve till intraspinal administration is employed.

In order to collect the total experiences gained concerning streptomycin therapy, two weeks ago a conference was held in New York of the physicians in Europe and U.S.A. who have treated most cases of tuberculosis, and it is to be hoped that when the transactions of this conference are published we shall get answers to the above questions or to others, with guiding principles for our management of the cases.

#### *A. Lichtenstein (Sweden).*

emphasized that even though the bacteriological examinations are of the greatest importance to the diagnosis as well as to the control of the course of the case it still is the clinical estimates that are decisive in the evaluation of a given treatment. In cases of tuberculous meningitis an observation period of at least 1 year is necessary.

*From The Children's Department, Rikshospitalet, Oslo.  
Head: Professor Leif Salomonsen.*

## **FOUR CASES OF HEREDOPATHIA ATACTICA POLY- NEURITIFORMIS (REFSUM) IN CHILDREN**

By

**LEIF SALOMONSEN and MARIT SKATVEDT (Norway).**

*Authors' abstract.*

During spring 1947 4 children were admitted to the children's Department of the Rikshospital, Oslo, suffering from a disease which we have not previously found described in children. All four were about 8 years old. Nos. 1 and 2 are twins, sister and brother. Their father's mother and their mother's grandfather were siblings. No. 3, a boy has no siblings; we have not found any consanguinity between his parents. No. 4 is a girl, her parents are first cousins. Her father has a daughter in another marriage; she is healthy. The medical history is similar for all four patients. In the first 3 the symptoms began at the age of 7 years, and in no. 4, at the age of 4. They began insidiously with loss of appetite, unsteady gait, dry skin and diminution of hearing. On admission to hospital they were all very thin. Their walking was atactic, their skin dry, desquamative with several scratching marks. No abnormal pigmentation. On ophthalmoscopy an atypical retinitis pigmentosa was found. The vision and the visual fields were normal. A slight degree of hemeralopia was present in pts. nos. 2, 3 and 4. Pt. no. 1 was not examined. All four children had diminution of hearing of the neurogenic type, nos. 2 and 3, the boys, in a moderate degree. No. 1 became deaf some months after her first admission to hospital. No. 4 had been deaf since she was 5 years old. There was muscular atrophy in the arms and legs, increasing distally. The deep reflexes were absent. Plantar and abdominal reflexes were normal. Sensibility was normal. No rigidity could be found. The first 3 patients had slight ataxia,

no. 4 severe ataxia. The spinal fluid contained normal amounts of cells, but total protein values ranged from 1/50+ to 1/460+, globulin 1/5+ to 1/16+. Ecg: The P-Q, the QRS and the QT values were all at the upper limit of normal or above the limit according to Ashman and Hull's tables.

The first 3 patients showed normal intelligence, no. 4 was a little demented, but she had been deaf 3 years at the time we saw her, and she remembered all the words she had learned before she lost her hearing. Wassermann reaction, blood count, blood electrolytes, cholesterol-values: normal.

At first we thought this might be a complex B-avitaminosis and we treated all four patients with big doses of all the vitamins B available, which we administered perorally and in injections, without any effect. The lacking effect on the skin symptoms speaks strongly against any pellagra component.

The later course of the disease showed some remissions (as one often sees in hereditary degenerative diseases in the central nervous system). During autumn and winter 1947 the pareses diminished in pts. nos. 2 and 3, with a relapse after parotitis in no. 3. Hearing diminished gradually in both. No. 4 became much worse in autumn 1947. She was almost paralytic, her skin was described by her father as being like the skin of a crocodile and she was extremely thin, but before Christmas her condition started to improve (she was stuffed with eggs, cod liver oil, cream and pork) and when we saw her again in spring 1948, she had gained 10 kg. and her skin was smooth. Her patellar reflexes had changed from extinct to hyperactive, and the Achillesreflexes were present. She was extremely atactic and could not walk without support. She was completely deaf as before.

The condition of the girl twin (Pt. no. 1) became gradually worse in autumn 1947. Her subcutaneous fat disappeared almost completely and she could hardly lift a hand or foot. Her skin became paper-thin, atrophic. She died cachectic. The most important findings on post-mortem examination (described by Dr. Cammermeyer) were: Fibrotic thickened leptomeninges with fat macrophages. Moderate degeneration of

the peripheral nerves with retrograde changes of the motor neurones in the spinal cord. Degeneration of olivocerebellar tracts homo- and contralaterally. Marchi-positive fat in moderate degree in nerve-cells and ependyma.

**Summary:** We have here a recessive hereditary disease which began in the age of 4-7 years, with loss of appetite, unsteady gait and increasing loss of hearing. On examination of the patients we find a moderate degree of retinitis pigmentosa, ataxia and a polyneuritis-like picture with abolished deep reflexes. The spinal fluid showed albumino-cytologic dissociation i. e., normal amount of cells and increased amount of protein. Eeg: Long extra systole. No decrease in the intelligence during the observation time.

Which disease is this? The skin symptoms, the polyneuritis and the diminution of hearing might point to a B-avitaminosis. But the spinal fluid values, the retinitis and the lack of improvement after treatment with vitamins B, do not support this diagnosis. The juvenile form of amaurotic idiocy may show cerebellar atactic symptoms and be combined with retinitis pigmentosa. This diagnosis is gainsaid by the lack of diminution of vision, no progressive dementia and lack of convulsions. Deafness, the high degree of hyperalbuminosis in the spinal fluid and electrocardiographic changes have not been described in this disease. The clinical picture may show some likeness to the hereditary ataxias and remind of an atypical form of Friedreich's ataxia. But this is gainsaid by the lack of speech disturbances and absence of deformities in the skeletal system. Retinitis is usually not seen in Friedreich's ataxia.

In 1946 the Norwegian neurologist Refsum described a syndrome which had not been reported previously. He called the syndrome: Heredopathia atactica polyneuritiformis. He found 5 cases, all at the age of 20-40 years.

They had hemeralopia with concentric limitation of the field of vision and retinitis pigmentosa, ataxia of the cerebellar type, distally increasing pareses of the arms and legs with muscular atrophy, muscular areflexia and a marked rise of the albumin and globulin content in the cerebrospinal fluid

with normal cell count. Inconstantly he found diminution of hearing and pathologic electrocardiogram. The disease was familial, most probably of a simple recessive mode of hereditary transmission.

This conforms so well with the findings in our patients that we must consider it the same disease. The post-mortem examination of our patient also conforms with Refsum's cases.

Heredopathia atactica polyneuritiformis in children has not hitherto been described. The pathologic-anatomic picture indicates that the disease belongs to the lipoidoses and thus is related to familial amaurotic idiocy and Niemann-Pick's disease.

#### DISCUSSION

*Erik Godtfredsen (Denmark).*

The 4 cases described by Professor Salomonsen and Dr. Skatvedt correspond closely to the Refsum syndrome — heredopathia atactica polyneuritiformis — in which retinal pigmentoid dystrophy is one of the cardinal symptoms. For several reasons the term "retinitis pigmentosa" is inadequate, and now replaced by ophthalmologists by dystrophia pigmentosa retinae, which gives a better expression for the abiotrophic character of the lesion, which is also evident from the nature of the other cardinal symptoms. The combination of retinal pigmental dystrophy and deafness is not characteristic of the Refsum syndrome, being encountered also in several other forms of abiotrophy (deaf-muteness, genuine pigmentary dystrophy, etc.) where mesencephalic localization is suggested.

The cases here described fit very well in the series of new ophthalmo-pediatric syndromes established in more recent years. Here it will suffice to remind of the comprehensive congenital syndrome with eye symptoms (cataract, microphthalmus, etc.), various malformations of the heart, disturbances of hearing, etc., that have been observed in children whose mothers had rubella in the first months of pregnancy. Thus the rubella syndrome presents many points of resemblance to the Refsum syndrome (eye, ear and heart symptoms), but the late manifestation of the cases mentioned here presumably excludes rubella. Another new and important clinical picture is brought about by infection with the highly differentiated protozoon Toxoplasma, which, after a primary influenza-like affection of the pregnant woman, passes through the placenta, and in

the child produces intra-uterinely a generalized infection. The cardinal symptoms are encephalomyelitis (microcephaly, epilepsy, idiocy, areas of calcification in the choroid plexus), eye symptoms in the form of chorioretinitis, massive defects of hearing, etc. Serologically, toxoplasma infection can be demonstrated by a complement fixation test. Thus, also this toxoplasmosis presents some points of resemblance to Refsum's disease, and it would be interesting to hear whether complement fixation tests were performed in the Norwegian cases.

The importance of knowledge of the diseases here mentioned is evident from the quite altered perspectives concerning infections disease in the first months of pregnancy as here we may institute treatment (chemotherapy, vaccination, etc.), possibly provoked, abortion (in order to prevent the birth of malformed children).

*Marit Skatvedt (Norway).*

Agglutination tests for toxoplasmosis were not performed, but roentgenography of the skull was normal in all the cases. None of the patients' mothers had had rubella during pregnancy.

*From The Children's Department, Rikshospitalet, Oslo.  
Head: Professor L. Salomonsen.*

**CONGENITAL PRECOCIOUS SYPHILIS TREATED WITH  
SPIROCID IN THE FIRST YEAR OF LIFE\*)**

*A follow-up examination.*

By

**GUNNAR NYHUS, (Norway).**

*Author's abstract.*

During the period 1929 to 1946 a total of 34 infants were treated adequately with spirocid at the Children's Department, Rikshospitalet, Oslo. The total quantity of spirocid administered varied between 5 and 80 grams. No definite grave complications occurred. 30 of these infants came for control from 2 to 18 years after the treatment had been terminated, one of whom had positive seroreactions and positive Wassermann's reaction in spinal fluid. This patient had not turned up for the stipulated control. All remaining patients were healthy except for two who had been exposed to traumatic brain injury at birth, and who had spastic paraplegia of the lower extremities. One of these was normally developed psychically, the other was an epileptic and an idiot. 4 of 23 possible cases had Hutchinson teeth. The examinations of vision and audition gave negative findings in all, as did also blood count and sedimentation rate. No skull changes. The I. Q. examination demonstrated 16 patients with normal I. Q., 8 backward, 5 feeble-minded and 1 idiot. Several of the backward patients had an I. Q. close to the normal. Psychical defects were demonstrated in the majority of the parents of the psychically retarded children. Poor inheritance, therefore, may be the cause of the reduced intelligence of these children with congenital syphilis. Spirocid administered in adequate doses to infants must be regarded as an equally effective anti-syphilitic as other recognized agents.

\*) A complete report on this material will be published subsequently in *Acta Paediatrica*.

*From the Children's Department, Rikshospitalet, Oslo.  
Head: Professor Leif Salomonsen.*

## SEPSIS NEONATORUM

By  
**HENRIK HAGELSTEN (Norway).**  
*Author's abstract.*

In this connection sepsis neonatorum (S. N.) is understood to be a septicemia or a septico-pyemia in the first 4 weeks of child life.

With the improved hygiene of infancy one might thus expect S. N. to become more and more rare. The cases from our hospital do not, however, give this impression.

During the 20 years from 1925 to 1944, 21 children under 4 weeks of age were treated under the diagnosis sepsis, i. e. about 1 case per year. In 1945 4 cases were treated, in 1946 9 cases and in 1947 11 cases.

An analysis of the 20 cases treated in 1946 and 1947 indicates that the entrance of the infection in 16 cases presumably has been the umbilicus, which was found to be discharging and purulent.

Immediately on admission a blood culture was taken in 16 cases out of 20. In 7 cases growth of hemolytic streptococci was obtained and in 3 cases growth of staphylococcus aureus. In 6 cases there was no growth in the blood culture, but a few of these had been treated with penicillin prior to admission.

The hemogram was in most cases characteristic with greatly increased SR., distinct leucocytosis and considerable increase in non-segmented polymorphonuclear leucocytes.

During the treatment the hemogram often changes surprisingly quickly and is in our opinion, a very good indicator for how long treatment should be continued.

In 14 cases one or more pyemic metastases with abscesses

were found, and in 7 cases an osteomyelitis were found. 2 of these patients had a subluxation of the hip joint caused by osteomyelitis with necrosis of caput femoris.

2 patients, discharged free of symptoms, have later developed a Banti's syndrome with swelling of the spleen and varices of the oesophagus.

The principle for the treatment has been to give penicillin as soon as the clinical diagnosis of S. N. was made, without awaiting the bacteriological verification of the diagnosis. Usually 10,000 I. U. were given as an initial dose, then 5000 units every 3 hours.

It has been difficult to draw any conclusion as to how long the treatment ought to be continued. In the beginning we undoubtedly discontinued the penicillin treatment too soon and got recurrences. The last couple of years we have continued the treatment for a fortnight and only terminated it when control of the hemogram showed normal conditions and the patient was afebrile, X-ray examination no longer showed any signs of metastases in the bone system, and the patient thrived and showed a steady increase in weight.

Penicillin has always been given parenterally. *Henderson* and *Mc.Adam* have shown that in infants under 4 weeks of age one can ensure a therapeutical concentration in serum after penicillin given perorally. This will facilitate the treatment.

The prognosis of S. N. was previously fatal. Since we started systematically to use penicillin the results of the treatment are satisfactory. Of our 20 cases treated in 1946 and 1947, 13 have been discharged free from symptoms, 4 are cured, but with sequelae osteomyelitis, 1 was improved and 2 have died.

#### DISCUSSION

*T. Salmi (Finland).*

In Finland, during the war, we had many cases of sepsis neonatorum. In particular pemphigus neonatorum appeared in severe septic form. Now when the general living standard, soap supply,

etc. has improved, the condition is quite different, and these diseases are very rare.

*Knud Bojlén (Denmark).*

It may be appropriate to call attention to the circumstance that sepsis neonatorum may appear under the clinical picture of tetanus neonatorum (cf. Ugeskr. f. læger 1935, no. 30, page 783), and that bacteria other than tetanus bacilli may give rise to muscular rigidity and convulsions (symptomatic tetanus).

Every year here in Denmark a rather great number of cases of tetanus neonatorum are notified. But, as a diagnosis is verified bacteriologically but seldom, nothing definite may be said about the etiology in these cases. A priori I am inclined to think that a greater majority of the notified cases have been instances of symptomatic tetanus.

For the sake of certainty, however, it seems advisable to immunize all pregnant women with tetanus toxoid or, if they have not already been vaccinated against diphtheria, with a mixture of diphtheria and tetanus vaccine (cf. Ugeskr. f. læger 1947, no. 30, page 403).

*A. Wallgren (Sweden).*

We generally associate the concept of sepsis neonatorum with cases presenting signs of blood infection or clinical signs of the infection spreading by way of the blood stream. No doubt, a good many of the cases mentioned by Dr. Hagelsteen belong to this category, but it seems to me that in several cases the criteria of blood infection are absent or at any rate not conspicuous, and these cases probably correspond to those Dr. Muhl later will deal with as instances of infections in the newborn.

In the Norrtull Hospital no accumulation of infections in the newborn has occurred if we leave pemphigus neonatorum out of consideration. In Sweden tetanus neonatorum is exceedingly rare, and I have seen only one definite case of this disease in 25 years. To me it seems peculiar if the disease in a country of such high hygienic standard as Denmark would be so common that prophylactic tetanus vaccination of pregnant women would be indicated and rational.

*From Flensburgska Vårdanstalten, Malmö.  
Head: Professor G. Muhl.*

**ON PROPHYLACTIC AND EARLY TREATMENT OF  
INFECTIONS IN NEWBORN, ESPECIALLY  
PREMATURE CHILDREN**

By  
**GRETA MUHL (Sweden)**  
*Author's abstract.*

The fact that the so-called early mortality in recent years has shown a tendency to increase, although the infant mortality on the whole has been decreasing makes it important for the obstetricians as well as for the pediatricians to combat it. The pediatricians might be able, among other things, to contribute hereto by trying to prevent the development of infections threatening the life of the newborn or, if this be impossible, to treat them as early as practicable. These infections are not so frequent as in the pre-aseptic time, it is true, but they do occur and appear to be increasing again. In particular, premature children with slight natural immunity are threatened by this danger, and in these children an early diagnosis is often difficult.

Previously we met with such early infections in the newborn but exceptionally. From 1944, however, we have had to treat a not inconsiderable number of such cases, transferred from the Lying-in Dep. of the Malmö General Hospital to the Flensburgska Children's Hospital, after 1945 usually at the age of 4-5 days and before this often at an age of 1-3 days. While previously infections in premature children in the pediatric clinic chiefly were nosocomial, they are now chiefly neonatal, which probably is connected with the local and personal conditions in the obstetric department; and while the mortality from nosocomial infections decreases on account of the new chemotherapeutics and antibiotics, the mor-

tality for the premature children is now ascribable almost exclusively to the neonatal infections. If the treatment of these cases be not instituted before the appearance of distinct clinical symptoms, it will often be too late.

We therefore have tried to arrive at an earlier diagnosis and treatment, and thus we have found it useful to examine the white blood picture, which often has proved to react with an increase — above all, in the number of polynuclears — before clinical symptoms have yet appeared; and thus we have been able in many cases to institute the treatment earlier than we would have done otherwise.

As now, however, the premature children generally are not transferred to the Children's Hospital before the age of 5-7 days, we suggested — and the Lying-in Hospital adopted our plan towards the end of 1947 — to carry through a prophylactic treatment of the children who are primarily disposed to infections, namely: the asphyxiated children, those who have aspirated, and those who are sluggish after injury to the brain or other birth injuries. Indeed, above all, it is such children who acquire early pulmonary affections, and in the present material as well as in other materials these lesions appear to predominate among the neonatal infections. This category of particularly threatened newborn ought to include also the very small children, weighing under 1500 g. at birth, as they have proved to be particularly susceptible.

The result of this has been encouraging. The mortality for the infected newborn has decreased from 78.5 % in 1944 to 37.5 %, 22.2 %, 15.8 % and 14.3 % in the following years respectively.

#### DISCUSSION

##### *Gunnel Melin (Sweden).*

Investigations carried out in two obstetrical clinics in Stockholm 1947 showed that pathogenic strains of *staphylococcus aureus* occurred in the upper air passages in the newborn in about 80 % in both departments. Here, then, the two departments showed no difference in this respect although an epidemic of pemphigus neonatorum appeared in one of them, while in the other department

all the children were well. Similar observations have been reported from U. S. A. and England (e. g., *Allison*). The occurrence of pathogenic staphylococci in the upper air passages in newborn with acute infections may therefore not offhand be assigned etiological significance. Complementary antibody examinations ought to be performed.

On account of the frequent occurrence of *staphylococcus aureus* strains resistant to sulfonamide and penicillin it is advisable if possible, to determine the resistance of the bacteria obtained before institution of treatment.

*From the Pediatric Clinic at Norrtull's Sjukhus, Stockholm.  
Head: Professor A. Wallgren.*

## THE RÔLE OF HUMAN MILK IN THE TRANSMISSION OF ANTIBODIES\*)

By  
**BO VAHLQUIST (Sweden).**

*Author's abstract.*

Antibodies may be transmitted to the offspring in two ways either in utero with the blood or after parturition with the milk. The main route is different in different species.

In man the placenta is permeable to antibodies and the concentration is for many types of antibodies the same in the blood of the newborn as in the blood of the mother.

The antibody contents of the colostrum and the milk reflect those of the mother's blood but the concentrations are as a rule much lower.

It is still a matter of discussion to which extent the infant may absorb the antibodies offered with the milk. In collaboration with my colleague dr. Högstedt I have performed experiments dealing with the absorption of diphtheria antibodies. High-titer homologous serum was given for several days in amounts varying between 25 and 150 A. U. per kilogram of body weight. Two groups of children were investigated. In one of these the children were all newborn and the antitoxin was administered from the first to the fifth day of life. Absorption could be demonstrated in 9 cases out of 13, but the amount absorbed never exceeded 0.3 % of that given. In 14 infants after the newborn period absorption could be traced only in two cases and in minute amounts. In 2 of these 14 cases the antitoxin was given with duodenal tube, and in 2 of the others for a longer period (14 days).

\*) Detailed figures for the results will be published elsewhere.

## DISCUSSION

*B. Broman (Sweden).*

Ever since Witebsky (Buffalo) in 1942 demonstrated the occurrence of Rh-antibodies in breast milk, the opinion is generally held that infants suffering from erythroblastosis should not take their mother's breast.

Rh-antibodies in a non-converted state are considered to be absorbed directly from the intestinal tract of the child and to haemolyze the child's erythrocytes. No direct proof of such a passage of Rh-antibodies has yet been furnished. Cases have, however been reported in which an infant suffering from erythroblastosis was not put to its mother's breast until it was two weeks old and anaemia then developed in immediate connexion with suckling. In most clinics, therefore, the mothers are not permitted to suckle such infants.

Owing to their relatively slight interest in lactation, American investigators have not attempted to any great extent to investigate this problem in detail. In Europe, on the other hand, interest in it has been greater.

Thus, towards the end of 1947, Cathie reported a number of experiments from the Great Ormond St. Hospital in London with the oral administration of Rh-antibodies to adults and children. In none of these experiments could Rh-antibodies be demonstrated in the circulating blood of the experimental subjects. The series did not, however, include any very newborn infants.

In order to complete the investigations carried out by Cathie, and in connexion with Vahlquist's studies on antibodies, I have performed a number of experiments with the administration of Rh-antibodies to newborns. Before reporting my findings, however, it is appropriate briefly to mention the different types of Rh-antibodies.

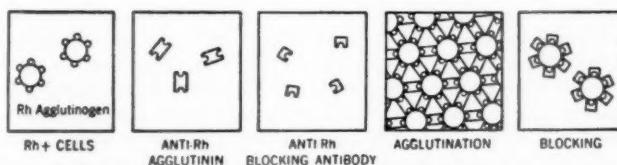


Fig. 1. Diagrammatic representation of Rh-agglutination and blocking reactions according to A. S. Wiener.

Fig. 1 shows schematically, after Wiener, how the appearance of the agglutinating and blocking Rh-antibodies may be envisaged. Of these, we are now aware that the blocking antibodies are of the

greater clinical significance. I have had occasion in one case to demonstrate that this antibody is able to pass more easily through the placenta.

*Pedigree of an Rh-immunized Woman with an Rh-positive heterozygote Husband.*

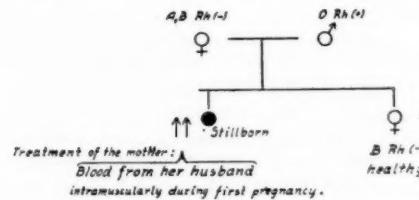


Fig. 2.

*Agglutination and Conglutination Tests on Maternal and Infant Serums on the day of Birth. Previously Rh-immunized Mother, Rh-negative Infant.*

Mother group A, B Rh(+) Rh-antibodies from a previous pregnancy	Agglutination	Test	cells	Undil.	1:2	1:4	1:8	1:16	1:32	1:64	1:128	1:256	1:512
		OR <sub>2</sub> r	+++	+++	+++	+++	+++	++	++	++	(+)	-	-
		OR'r	+++	+++	+++	+++	+++	+++	+++	+++	(+)	-	-
Infant group B Rh(-) cord blood	Agglutination	OR <sub>2</sub> r	-	-	-	-	-	-	-	-	-	-	-
		OR'r	-	-	-	-	-	-	-	-	-	-	-
	Conglutination	OR <sub>2</sub> r	+++	+++	+++	+++	+++	+++	+++	+++	++(+)	++(+)	-
		OR'r	+++	+++	+++	+++	+++	+++	+++	+++	+	+	-

Fig. 3.

As shown in Fig. 2, this is the case of an Rh-negative and Rh-immunized woman whose first child died of erythroblastosis foetalis. The husband was heterozygous Rh-positive and a second child was Rh-negative and healthy. Fig. 2 shows that although the mother had agglutinating Rh-antibodies of high titre in her serum, no such antibodies could be demonstrated in serum from the umbilical cord of the child. On the other hand, by means of conglutination, blocking antibodies of high titre were shown to be present.

In the course of 3½ days, two newborn Rh-negative infants, weighing 3 and 4 kg, were given by mouth 90-100 cc. of serum containing blocking Rh-antibodies (titre: 1:32 and 1:12). No Rh-antibodies could be demonstrated in venous blood from these infants immediately after the discontinuance of the treatment. (Both

the albumin method and Coombs' indirect reaction were used in the investigation.)

From experience gained hitherto concerning the effects of Rh-antibodies on oral administration, the following conclusion can be drawn: *The occurrence of Rh-antibodies in the breast milk of the mother is, as a rule, no reason to forbid her to suckle her child.*

*A. Lichtenstein (Sweden)*

reported a case of typhoid immediately after delivery in a sucking mother whose child remained clinically well. The mother's milk as well as the child's serum showed just as high agglutinative titer as did the mother's serum.

*P. W. Bræstrup (Denmark).*

Has simultaneous examination of umbilical cord blood and venous blood from the newborn been demonstrated to give concordant results?

*T. Salmi (Finland).*

Since March 1948 the Åbo mother's milk center has stored the not immediately distributed mother's milk at very low temperature, up to the present, about 300 l milk.

The milk is stored in paraffined cartons of 250-300 cc. This size is practicable as the milk then may be consumed in small portions. The milk is brought to the boil, poured into the cartons and refrigerated at about —20° C. The milk melts at room temperature within 6-8 hours.

Since June 1948 this milk has been examined in the Åbo Children's Hospital in order to ascertain which changes may be demonstrated in the refrigerated milk and how the children react hereto.

The frozen and thawed milk has shown no change in smell and taste. Its reaction has been followed by weekly measurement of pH and found to remain between 6 and 7. No pathogenic bacteria could be demonstrated by control cultivation from the thawed milk. The C vitamin concentration has remained approximately unchanged after 2 months' storage.

The milk has mostly been given to premature children. Through observations on increase in weight the general condition, character of the feces, vomiting, and blood picture no abnormality could be demonstrated.

*Bo Vahlquist (Sweden).*

1. There is no difference between the antibody content of the blood of the umbilical vein and that of other vessels of the newborn.

2. It is quite possible to protect the offspring against diphtheria and tetanus by means of immunization of the pregnant women. In the present immunity situation in Sweden, however, the anti-toxin titer obtained is in many cases only moderate and of short duration. In Sweden, anyway, I should not like to recommend large scale immunization of the pregnant women. But the situation may be different in other countries.

**SECTION II**

**SATURDAY, AUGUST 14.**

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*From the Pediatric Department, University Clinic  
at Rigshospitalet, Copenhagen.  
Head: Professor P. Plum.*

## WHAT IS THE ATTITUDE OF PEDIATRICS TO PSYCHOLOGICAL PROBLEMS OF CHILDHOOD?

By  
P. PLUM, (Denmark).  
*Author's abstract.*

Psychologic and psychiatric problems constitute an integral part of pediatrics. It is not practicable sharply to distinguish between psyche and soma. The nervous diseases of childhood fall within the following categories:

- A. Mental disturbances without somatic symptoms.
- B. Mental disturbances with resulting somatic functional symptoms.
- C. Mental disturbances with resulting organic changes.
- D. Mental disturbances complicating organic diseases.

Numerically these diseases play a very great rôle in pediatrics as well as in medicine. As an example of the last group, Little's disease may be mentioned.

Neither children's psychiatry nor pediatrics can cover the work to be done. We shall have to make use of the assistance of psychologists, and it is essential that the practising physicians be trained in such a way that they are able to do a great part of the task. In the Pediatric Department of the Rigshospital during the last 3 years we have cooperated regularly with psychologists, just like a varying number of students of psychology have been given clinical training in our department. We have been employing the Rorschach test and other tests to a large extent in the ward as well as in the out-

patient clinic. We think that a majority of the mental problems of childhood can and ought to be treated in pediatric departments, out-patient clinics, or child-guidance clinics, and that it is only a minor part of these children who require treatment in a psychiatric department.

Pediatrics ought to take the lead in the study of the laws governing the mental reactions of children.

*From Fuglebakken's Children's Hospital, Copenhagen.  
Head: V. Poulsen, M.D.*

## PSYCHOSOMATIC PEDIATRICS

By  
**SVEND HEINILD (Denmark).**  
*Author's abstract.*

### *Introduction.*

With references to the literature it is pointed out that connection between the emotions and pathophysiological changes in the organism has been realized for centuries. The advance made in our days consists in the fact that with our modern laboratory methods for examination we are able to demonstrate that in a normal subject the exposure to emotional insults may give extensive and, sometimes, deep changes in the organism — in the blood vessels and the glands of the skin, digestive organs, urogenital system, circulation of the blood, endocrine glands, etc. Repeated irritations of this kind may result in effects that are just as injurious to the organ in question as a genuine organic disease, infection or intoxication.

### *Writer's Investigations.*

The purpose has been to investigate how great a rôle is played by psychosomatic affections in a general, not specialized, pediatric clinic in Copenhagen (Fuglebakken Children's Hospital). Through a period of 15 months all children admitted at the age of 2 to 11 years and their relatives were questioned thoroughly about their milieu, and at the same time, general clinical and laboratory examinations were carried out. Thus it was found that in 112 out of 213 children a psychogenic, or a psychogenic-social factor constituted the essential etiological feature in the morbid conditions, or —

in other words — in 52 % of the patients of this age group the affection was of psychosomatic nature. These patients fall into three groups:

*Group I. Psychosomatic affections proper.*

Enuresis .....	34
" + encopresis .....	6
Anorexia .....	17
Abdominal colic .....	14
" " + hypersecretion	4
Encopresis .....	4
Diarrhea .....	4
Constipation .....	3
Tic .....	3
Asthma .....	2
Cephalalgia .....	2
Cardiac neurosis .....	1
Vertigo .....	1
	—
	95

*Group II. Disturbances of behavior with mental symptoms.*

Masturbation .....	3
Uneasiness and restlessness .....	3
Jactitation of the head .....	1
Nicotinism .....	1
Pyromania .....	1
Vagabondage .....	1
	—
	10

*Group III. Constitutionally organic lesions with mental symptoms.*

Mental debility .....	3
Adipositas .....	2
Psychopathy .....	1
Dyslexia .....	1
	—
	7

*Conclusions.*

Hitherto the development within pediatrics has been askew, with the main importance being attached to the somatic diseases and with relative underestimation of the psychogenic factors. It is our task now to establish an intensive study of child psychology and child psychiatry. In practice we have to advocate increased employment in pediatric clinics of a personnel with child-psychological training (infant pedagogues, social workers, and professional psychologists). In particular greater stress is to be laid on the training of nurses in child psychology. As pointed out, child-psychological problems are an integral part of the working field of every pediatrician. Therefore, it is highly advisable not to separate child psychiatry as an independent speciality within pediatrics.

*From the Pediatric Clinic at Kronprinsessan Lovisa's Children's Hospital, Stockholm.  
Head: Professor A. Lichtenstein.*

## INFANTILE ASTHMA AS A PSYCHOSOMATIC DISEASE

By  
**SIV GUNNARSON (Sweden).**

*Author's abstract.*

That nervous factors play a great rôle in bronchial asthma has long been known. Previously the problem was tackled chiefly by internists or by psychiatrists. In recent years the increasing interest in psychosomatic affections, with endeavors at cooperation between pediatricians and child psychiatrists, has brought about a more thorough study of asthma with parallel analyses of somatic as well as psychiatric-psychological aspects, and better therapeutic results have been reported by several authors.

In our hospital, infantile asthma has been studied thoroughly in the last 18 months through team work: the child is examined first in the somatic asthma clinic and then referred to the department of child-psychiatry. The treatment is planned in keeping with the findings from both of these examinations.

In the following an account will be given of the results of the mental examination. The material comprises 58 cases, 21 girls and 37 boys, all with normal faculties, many even in a high degree.

Table 1 gives some anamnestic data from which it is evident that mental diseases and neurotic conditions are just as habitual as are allergic diseases. Many children give a history of pronounced anorexia prior to the appearance of the asthma, and the same applies to disturbances of the sleep. In several cases the asthmatic stage was preceded by pavor nocturnus, which disappeared when the asthmatic attacks commenced.

*Table 1. Mental Examination of 58 Asthmatic Children.*  
*Anamnastic Data.*

Heredity:

For allergy .....	50 %
For mental illnesses and "nervousness".....	53,4 %

Psychosomatic symptoms *before* appearance of asthma:

Anorexia before 1 year of life .....	30 %
" after 1 " " "	38 %
" before and after.....	25 %
Pavor nocturnus or other disturbance of sleep	38 %

In our material we meet with a variegated group of different mental symptoms which largely may be divided into two groups:

Group I comprises children who are inhibited as to aggression. From early childhood these children have been accustomed to restraint and rarely give vent to their sentiments and aggressions. Occasionally this inhibition arises presumably from constitutional conditions: a strong ambition drives the children to strain every nerve. Sometimes the inhibitions are to be looked upon as injuries from the surroundings: even at an early stage the parents demand a high degree of selfcontrol. In many cases we may find a direct connection between inhibition of aggression and the asthmatic attack, which may appear in direct connection with the inhibition of aggression, especially in uncomfortable situations. As is shown by examples:

A boy who from infancy had presented certain allergic symptoms and showed a pronounced skin allergy to fish — "he had asthma as soon as there was fish in the house" — was forced by circumstances to live with a strict, hard, and demanding aunt. The patient hated his aunt but dared not show his aggressions. During the five years in which he lived with her he had continuously severe attacks of asthma, from which he often had to be hospitalized. Gradually it became obvious that the patient was better when away from home or when the aunt went away for a couple of days, and that sometimes he had an attack as soon as she stood in the door of his room.

As soon as the aunt was deprived of her legal guardianship and the boy was placed in the home of a kind-hearted relative where he was feeling emotionally well, the asthmatic attacks ceased completely, and now he has been free of symptoms for 2 years. He still does not eat fish but sits nicely at the table while the others eat it.

Group II — of mental symptoms presented by the children in this material — comprises various signs of pathological attachment to the mother. For their age these children are immature and dependent, with poor self-confidence, unable to do without the mother even for a relatively short time. On admission to the hospital, the separation from the mother elicits in the younger children some strikingly violent scenes of despair, which often are followed by some asthmatic trouble.

In a boy, 12 years old, the asthmatic attacks commenced at the age of 6, simultaneously with the beginning of intense friction between the parents. The boy took the mother's part. Finally the parents were divorced and the mother and boy led a quiet life. Subsequently the mother had to take a job and the boy became very lonely. He was greatly attached to his mother, and often he would make a scene when she had to leave in the morning, although he was then 10 years old. — In the hospital, under play-therapy, the patient chose painting. He would continuously draw a harsh, ugly man's face, painting it black and crossing it out, etc. He further painted falling aeroplanes with swastika on the wings. The father was found to be of "Hitler type" — and obviously the face symbolized him, and the swastikas were symbols of his despotism. — While the painting therapy was going on, conditions improved for the mother, and matters were arranged so that she could be home when the boy returned from school. He was symptom-free through several months, and then he had a violent attack. His attitude towards his father proved to be ambivalent. He certainly hated his father, and his mother did not want him to visit the father, and he wanted to be loyal to the mother. But the father bribed the boy with money and invited him to the movies — a thing the mother could not af-

ford. The conflict in an acute situation of this kind elicited an attack. — Later on, the nature of the condition has been explained to the mother and she has realized it, so that now she tells the boy to visit his father — and he has been free from symptoms for 4 months.

*Table 2. Mental Examination of 58 Asthmatic Children.  
Mental Symptoms.*

	Number of children	Per cent
Aggression-inhibited .....	29	50 %
Pathol. attachment to the mother ..	12	20,7 %
Aggression-inhibited + mother- attached .....	6	10,4 %
Mental symptoms of other character ..	5	8,6 %
No mental symptoms .....	12	20,7 %

Table 2 shows the percentage of the various mental symptoms in the present material. Absence of mental symptoms was found only in 20 % of the material.

The percentage of considerable injuries from the environment is high, 67 %. In 22 % only, a milieu injury was not proven.

Usually the asthmatic attacks have commenced at the age of 2-4 years, which corresponds to the first age of negativity.

Many of the children show positive reactions for skin allergy of various forms; and this applies also to the children who have improved distinctly from sanation of their environment, sometimes combined with psychotherapy. We find about the same percentage of positive and negative children within the groups with different mental symptoms.

Summarizing this investigation it may be said: Even prior to the first appearance of the asthma, the asthmatic children show various neurolabile symptoms. Aggression inhibitions within the family and a pathological attachment to the mother appear to be particularly important factors in the origin of asthma in neurolabile children, both in children in whom a

constitutionally somatic allergy can be demonstrated, and in children giving negative results in tests for somatic allergy. Attempts to liberate these mental inhibitions should thus constitute an important part of the treatment, and it is reasonable to expect better therapeutic results from a combination of a somatic and mental therapy.

The observation period is not yet sufficiently long for a critical estimation of the therapeutic results in our material. But to us they seem particularly encouraging when somatic treatment is combined with psychotherapy.

#### DISCUSSION

*Justus Ström (Sweden).*

The mental care of children is a most important social-medical question. In Sweden, for some years we have had a state-supported organization, which now has been established in 3 counties. In Värmland, where it has advanced farthest, it has been overrun with work even from the very start, although only remiss cases are admitted. The prophylactic mental care of children has to be carried out in a wider field and become an important part of the state's preventive care of children. This presupposes that our pediatricians as well as medical officers who are in charge of our children's welfare centers acquire an entirely different insight into these matters and really commence to take interest in the mental-hygienic work. This also applies to our specially trained children's nurses and district nurses. But no real change may be realized before the training is reorganized so that child psychology and psychiatry, pedagogics and principles of education become a considerably greater part of their training than is now the case.

*A. Wallgren (Sweden).*

Undoubtedly we can all subscribe to the wishes concerning the requirement of better training in psychology and psychiatry for physicians as have been advanced by Professor Plum and Dr. Heinild. In our country we have gone another way when it comes to expert child-psychiatric-cooperation than adopted in Denmark.

In Sweden it was pediatricians who did the pioneer work and took the lead. I wish to call to mind the fact that already 20 years ago Jundell planned a child-psychiatric policlinic, which was instituted while Wernstedt was chief of the Norrtull Clinic.

This development has now advanced further, and at present we have a child-psychiatric department and polyclinic in both of our teaching clinics in Stockholm with specially trained child-psychiatrists, child-psychologists and assistants; and it has been proposed to extend the scope of this activity with additional physicians and other associates. In the past year, in Stockholm we have given a short course in child-psychology and some lectures in child-psychiatry for the medical students, as a start.

Whether a psychiatrist or pediatrician has charge of the psychiatric child-clientele, I think, plays no particular rôle. The important point is that the physician concerned has sufficient training and experience in pediatrics, psychiatrics and child-psychopathology and that he is interested in, and suitable for, the task.

*Zaida Eriksson-Lihr (Finland).*

For a good many years the question about the significance of the psychogenic factors to the origin and development of allergic diseases has been a subject of lively discussion, and sometimes it has led to excess in one direction or the other.

The more the technique of examination regarding allergic diseases has developed, the more have the psychogenic factors had to give way to entirely somatic causal factors in the genesis of allergic diseases, in particular infantile asthma, while they still remain as a significant secondary factor.

The material that Dr. Siv Gunnarson has presented today might make it appear that the neuro-psychic complex in a high percentage of cases has been the primarily eliciting factor in infantile asthma. Keeping in mind that about 60 % of children suffering from asthma have had allergic eczema prior to their asthmatic attacks, and considering the suffering these children go through in the 1-2 years the eczema has lasted, it is not to be wondered if most asthmatic children show mental disturbances, fright psychoses, excessive attachment to the mother, etc., which also may elicit attacks in these allergic children.

Even though modern research in allergy chiefly refers the neuro-psychic factors to the so-called secondary factors in the genesis of infantile asthma, they still, of course, will have to be dealt with adequately, and often this has to be done for a long time after the somatic treatment — e. g. elimination of allergens, desensitization, treatment of infections a. s. o. — is finished.

*A. Lichtenstein (Sweden).*

Child-psychology and child-psychopathology have to be looked upon as an integrant part of pediatrics. Practically in every case

the pediatrician is faced by some psychologic problem. It is only natural that the psychosomatic diseases attract increasing interest. All this will have to be taken into consideration in a way entirely different from previously in the instruction and training of the coming pediatricians.

We are here dealing with a border zone between pediatrics and psychiatrics that cannot be left entirely to psychiatrists. Every fairly large children's hospital or department requires a psychologic-psychiatric team that cooperates closely with the department. This team should consist at least of a physician trained in pediatrics, psychology and psychiatry, an assistant physician, a psychologist, a social worker and a secretary. This is the minimum if the clinical as well as the polyclinical work is to be covered in these very time-consuming cases.

## SOME POINTS OF VIEW ON THE PROBLEMS OF MENTAL HYGIENE IN SCHOOLS

By

C. W. HERLITZ (Stockholm, Sweden).

*Author's abstract.*

A matter which in recent times has especially attracted the attention of pedagogues and doctors is the care of pupils with *disturbances in behaviour*. This refers to those who without "having any difficulty in learning" prove to be psychically unusual in other respects and show signs of arrested development or injury in emotional respects. Experience teaches that persons who are not doctors sometimes find it a little difficult to understand why the assistance of medical experts must necessarily be resorted to in schools for the diagnosis and planning of the treatment in these cases. These pupils, they say, are not, or need not, be "ill". As far as possible the psycholabile children must be recognized as such at school and quickly be given adequate treatment in cooperation with their homes. This can only be done satisfactorily if medical knowledge is available at the earliest stage.

In the case of the pupils with disturbances in behaviour the question of the distribution of work among teachers, school psychologists, school doctors and advisory bureaus has proved to be particularly urgent in many places. It appears readily to suggest itself to the person without medical knowledge to try to divide the pupils into those with "slight" and those with "severe" disturbances in behaviour and to think that it is appropriate that the slight cases should be taken in hand by pedagogues and psychologists without any contact with the doctors, while in the severe cases the doctors should be consulted. In this connection I need not go closely into the

reasons why I cannot consider this argument acceptable. It seems to me more appropriate, in point of principle and from a practical point of view, to divide up those with disturbances in behaviour into temporary and non-temporary. As a rule the pupils who exhibit disturbances in behaviour of a non-temporary nature should be the object of consultations between doctors and pedagogues. However, this roughly schematic way of looking at the matter is not entirely satisfactory either, as naturally "temporary" disturbances which may also appear may be of such a nature that the assistance of the doctors at the investigations may be necessary.

It is of the greatest importance that the doctors should point out clearly that symptoms of psycholability can very often be traced back to purely physical conditions of illness and debility, sometimes caused by bad external conditions of milieu, such as unhygienic dwellings, unsuitable food and too little sleep. To the person who is not a doctor such an explanation often makes it more understandable why school doctors and school nurses must be considered to have great and important tasks to perform in this field. Doctors and nurses who are not specially trained in the mental-hygienic sphere can also do valuable work here.

Special attention should be devoted to the manner of sending pupils with disturbances in behaviour from teachers to school psychologists or doctors and between school psychologists and doctors. In certain places the procedure is that the teachers send the children to school psychologists, who subsequently, when they themselves find there is reason to do so, initiate consultations with school doctors, child psychiatrists or advisory bureaus. The children in question may exhibit, for example, restlessness, nervous fear, aggressivity, night-terrors, nail-biting, enuresis, stammering or so-called word-blindness. I cannot think that this organization of the work is to be recommended. My view is that *all* children who are sent by teachers to school psychologists on account of disturbances in behaviour ought also immediately to be examined by a doctor. It is appropriate that the teachers and school psychologists should first establish contact with the

school doctors and the latter with the children's private doctors. When necessary the children should be subsequently sent to child psychiatrists or advisory bureaus after agreement with the parents.

A further important mental-hygienic task in the schools is to take charge of children with *arrested intellectual development*. The children in the relief classes belong to the school's control children. It is important, as has been pointed out by doctors in the schools that, in addition to their intellectual inferiority, these children often exhibit arrested development or injuries within the emotional sphere or physical illness and debility. On that account, *inter alia*, these pupils must be the object of the special care, not only of the teachers but also of the doctors and nurses. No pupil should be placed in the relief class without consultation with school doctors or specially trained child psychiatrists, where such experts are available.

In order that the doctors, side by side with the teachers, may achieve valuable work in the sphere of mental hygiene, it is not only necessary that they should have good training, but also that they should have sufficient time at their disposal for their work in the schools. Assistance from special instances, such as child psychiatrists and advisory bureaus, ought by no means to be relied upon entirely, but, by means of a good basic medical training and a further training of school doctors, attempts must be made to see to it that their qualifications for the mental-hygienic work be as good as possible. Naturally the nurses ought also to be well orientated for their work in the service of psychic health. With regard to the teachers, it is of the greatest importance that, during their period of training, they should not only be orientated in normal psychology but also in the psychopathology of youth. In many places the teachers of biology are especially in need of medical courses which also deal with the problems of mental hygiene.

## MENTAL HYGIENE AND EDUCATION

By

E. GEDDA (Gothenburg, Sweden).

*Author's abstract.*

As medical officer of child hygiene in Gothenburg and as school physician, the author has met the questions of modern education and has almost been forced to take a stand and give his opinion.

Through many years he has then proposed "the golden middleway in education". The child must not be suppressed. As a member of mankind and as an individual it must have its freedom, its security, its "living room", toys and so on. But on the other hand, it must learn to respect its parents, its playmates, the law and the good, old customs. Otherwise it may get bad and selfish habits, perhaps more important than the complexes.

The paper ended with a table containing the results of two examinations (published in *Acta Pæd.* and *Nordisk Medicin*) on the frequency of nervous disturbances in children at a day-nursery (58 % of the children had such disturbances) and in children who have just begun school (age 7 years). Of these, 44 % had nervous disturbances of such a degree that the parents, without special questions from the school physician, told him of them.

The cases of nervous disturbances in children are so frequent that it is quite impossible to send them all to the few child-psychiatrists of our country. They must mainly be cared for by the physicians at the child hygienic institutions and schools.

## DISCUSSION

*Siv Gunnarson (Sweden).*

At the International Congress of Child Psychiatry now being held in London it has been emphasized from all sides — by child psychiatrists, analysts, and psychologists — that an unprincipled and lax bringing-up may be just as injurious to the child as a hard and non-understanding one. Children need certain guiding lines so as not to become insecure and feel unsafe. Unprincipled and lax bringing-up which does not convey any feeling of security to the child, may even give neurosis.

*From the Pediatric Department at the Central Hospital, Borås.  
Head: B. Söderling, M. D.*

BREAST FEEDING AND VOCATIONAL EMPLOYMENT  
IN AN INDUSTRIAL TOWN  
SOCIAL-PEDIATRIC STUDIES

By  
**BERTIL SÖDERLING (Sweden).**

*Author's abstract.*

The material consists of 405 mothers with infants and has been collected partly from the Children's Welfare Centres of Borås during the years of 1940—45 and partly from a private Mothers Home in the town. Owing to different purposes in view during the course of the investigation the material has been divided into three groups. The normal material comprises partly a selected, statistically adequate, material of 216 mothers who suckled their children, and who definitely had no employment during the time their children were receiving mother's milk, and partly from the annual dietarian reports from the Children's Welfare Centres. Generally the Children's Welfare Centres had a material of about 750—800 registrations per year and in Borås practically 100 per cent of all babies are registered there.

The first material, consisting of mothers with full-time outside employment (in the great majority of cases, in the textile and ready-made clothing industry) and with children of normal suckling age, has been collected from the period of 1940—1942 and comprises 236 cases. Of these mothers 102 had weaned their children before they returned to their work. Only 62 of the 236, *about 26 per cent* had been able to give the child breast milk for six months or longer. Against these 26 per cent, the normal material shows 69 per cent, and the annual reports, 60 per cent (the number in the annual

reports comprises naturally also women with outside employment, whilst the *pure* control material consists exclusively of mothers at the Home). If we disregard the number of cases who ceased suckling their children before they commenced or resumed their work, the relationship will be 62 of 134 = *about 46 per cent*. Furthermore, it was found that about half of the mothers who began their work about 6-8 weeks after delivery had children completely weaned within two months of commencement of work.

The second material — treated more statistically — consists of 94 whole-time employed feeding mothers from 1943 to 45 (so those mothers who ceased suckling their children before the commencement of work are not included). Work was commenced on an average 88 days after delivery, unmarried women after 77 days, married women after 93.4 days. One month after the commencement of the work there were altogether 32 or  $34 \pm 4.9\%$  without mother's milk. If we compare this material with that of the mothers in the normal material, who had at least some mother's milk for three months or more, the difference will be  $14.3 \pm 4.7\%$ , — a statistically significant difference. Five months after delivery the difference between the two materials will be  $21.4 \pm 5.3\%$  a statistically significant difference here too.

The most interesting proportion is however shown by the Mother's Home material consisting of 75 mothers from the Mother's Home of the Salvation Army at Borås and its activity from 1943 to 1948. The feeding mother with outside employment finds in this home an ideal background for her double duty of mother and factory worker. The only thing she has to do inside the home is to suckle the child and to give it as much personal care as possible. The 75 mothers began to work when their babies were on an average 63 days old. The vast majority of the mothers at this home were workers in the textile industry. When it was time for them to begin work again the average amount of mother's milk was 566 cc. per day. After *one month's work* the daily quantity of milk had fallen to 451 cc. and three children were then altogether without mother's milk. *Two months after* the commencement of

work, the average quantity of mother's milk was 347 cc. and then another 12 children were without milk, making a total of 15, or  $21.4 \pm 4.9$  per cent.

### **Summary.**

It might thus be inferred that in spite of considerable facilities and abundant help with work in a home, full-time employment away from home is generally a substantially unfavourable and often definitely destructive factor\*).

## **DISCUSSION**

### *P. Nordenfelt (Sweden).*

#### *Why are children under 2 years in a day-nursery?*

The attendance at the day-nurseries of Stockholm was investigated during the week of Dec. 1-7, 1947.

The material comprises 3063 children of 2749 mothers from 70 day-nurseries in Stockholm, that is, practically all of them.

The causes of the attendance at the day-nurseries are investigated a detailed questionnaire filled in by the matron.

Today time allows me merely to give an account of the reasons why children of up to 2 years attend day-nurseries. There are 535 children in this age-class.

From the tabulation it is evident that the main reason why lone mothers have their little children in day-nurseries is — as was to be expected in most of the cases — their social situation of being the sole bread-winner. Only 7 out of 180 gave some other reason. Of the nursery children in this age-class, 34 % had lone mothers as against 40 % for the entire material.

Of the married couples, 72 out of 354, or 20 %, have their infants in day-nurseries on account of various social conditions. In 25 of these cases the mother's income is certain, the father's uncertain, and in 23 cases illness or invalidity of either parent was given as the reason. In the cases we have to reckon that it is the income from the mother's work that the existence of the family is based upon, except in the cases where the mother is ill — 70 cases in the entire material.

In 2 cases another form of poor home is given as a reason; 6 give unsuitable family milieu as a reason, and 16 some other cause.

\* ) I beg to thank Dr. Kjell Möller for his valuable assistance with the statistical part of the study.

No doubt the last group of reasons covers also several cases of unsatisfactory dwelling.

In 70 % (249 out of 354) of the cases it is because of economical reasons that the married parents have their little children in day-nurseries. Of this number, 201 think that the family budget requires the wages of both parents; in 30 cases it has been a loan or debt for furnishing the home; in 8 cases, a study loan; in 8 cases, other economical reasons; and in 2 cases, the husband's obligations in respect of previous marriage or extramarital child.

18 of the married cases are recorded under the heading of "determined wish of the mother to keep working in spite of comfortable economy" as main reason for having her child at the day-nursery. Of these 18 women, 8 consider themselves unsuitable for housework, while 10 have had some other, not differentiated, reason. A majority of the latter give the mother's professional training as a reason. In 8 cases the cause has been pressure of social institutions and employers; and in 1 case long waiting time.

I am fully aware that the figures obtained in an investigation of this type are quite uncertain, and that they are to be taken only with reservation. The replies are subject to the influence of many psychological factors. In this investigation I have tried in some degree to reduce such sources of error by letting the matrons write the answers with the aid of their notes and personal knowledge of the family.

If we compare the distribution of the main reasons for the children under 2 years with those for the entire material, we find a surprising similarity of the two groups of figures, with merely insignificant differences as to individual details. We had expected to be able for the youngest children to trace a shift in the causes towards more severe social and economical conditions — in other words, stronger indications for admission. We had also expected that the percentage of lone mothers of children under 2 years would be higher than for the entire material, but as I have pointed out before, it is somewhat lower. Of the previous investigations it also is evident that in Stockholm the percentage of younger children attending day-nursery is lower than that of older children. But this is due entirely to the access to day-nurseries, for the waiting-lists of applicants are big in all age-classes, especially in the lower.

The drawbacks — from a mental as well as physical point of view — of the collective care in nurseries are greater for the children in the lower age-classes, in particular, under 2 years. This was realized long ago by pediatricians and by psychologists and in recent years, various investigations (e. g., in England and Sweden) have confirmed this view.

The present investigations indicate that the young mothers have not yet realized this, at any rate it has not brought about any decrease in the number of applications to the nurseries.

In order to reduce the number of children under 2 years in day-nurseries, I should like to suggest the following:

1. Restraint in building and equipping day-nurseries for children under 2 years. Seek other ways of helping mothers with little children (e. g., economical aid other than nursery care and more experiments with day care in private families, so-called foster day-homes). My investigation into the underlying causes shows that the great majority of the mothers need some form of help.
2. Give all day-nursery matrons such training and education that they might be able to give advice and assistance at least to some of the mothers and help them out of their difficulties in some way other than through nursery care. Possibly curators might be appointed who might be of assistance to the matrons in their activities. Conceivably such curators might have to visit mothers with children under 2 years before their admission to the nursery.

*From the Pediatric Clinic and Surgical Department at Kronprinsessan Lovisa's Children's Hospital, Stockholm.*

*Heads: Professor A. Lichtenstein and Ph. Sandblom, M. D.*

## ELECTRO-ENCEPHALOGRAPHY IN HEAD INJURIES IN CHILDREN

By

KARL-AXEL MELIN (Sweden).

*Author's abstract.*

The value of electro-encephalography to the diagnosis in acute head injuries and for the control of the healing in such cases has been evidenced by various authors (e. g., Williams & Denny-Brown, 1941, Hoefer, 1943, Puech & Fischgold, 1944, Dow, Ulett & Raaf, 1945, Jasper, Kershman & Elvidge, 1945).

Since 1947, this method has been employed in the Kronprinsessan Lovisa's Children's Hospital, where all children with acute injuries to the head were examined electro-encephalographically. Eighty children, aged 0-13 years, have been examined, and on studying this material I find in a great many cases a very good correlation between the degree of the injury and the EEG findings. In cases without immediate data on the injury or where the clinical findings are dubious, the EEG has been taken as decisive of the treatment. In those cases where continuous control examinations could be carried out during the period of illness the EEG changes have subsided gradually, though as a rule more slowly than the clinical signs of the injury.

In altogether 5 children the pathological EEG findings persisted for 1-3 months after the injury. In 2 of these patients also clinical symptoms were present in the form of headache, irritability, failing concentration. Localized EEG findings occurred in 12 patients, in 9 of whom there was a fracture of the skull — always within the region where the abnormal EEG findings were localized. According to the experiences from

adults, these patients should be followed very closely, as it is just among such cases that posttraumatic epilepsy turns up.

EEG completes essentially the clinical examination in cases of injury to the head in children. By means of EEG the character and extent of the injury may be estimated with greater certainty, and its healing may be controlled. It is to be emphasized, however, that EEG must not take the place of a thorough clinical study of the patients. The best results are obtained through close collaboration between the clinician and the EEG laboratory.

*From the Children's Department, Rikshospitalet, Oslo.  
Head: Professor Leif Salomonsen.*

**CELIAC DISEASE. SOME EXPERIENCE ACHIEVED FROM  
74 PATIENTS TREATED IN THE CHILDREN'S  
DEPARTMENT OF RIKSHOSPITALET, OSLO**

By  
**ANDERS THO (Norway).**  
*Author's abstract.*

Since the Jan. 1, 1940, 74 patients suffering from celiac disease have been treated in the Children's Department of Rikshospitalet. The most important results achieved by examining this material will be briefly presented here.

The 74 patients counted 33 boys and 41 girls. Table 1 gives a view of the number of cases observed each year.

**Table 1.**

Year:	Number of patients:
1940 .....	7
1941 .....	5
1942 .....	3
1943 .....	3
1944 .....	6
1945 .....	6
1946 .....	12
1947 .....	21
1948 (the first six months) .....	11

We notice the increasing incidence of the disease after the war. A similar increase, as will be known, took place during the war in Denmark and Finland, too. It is to be noted that former breastfed infants are as frequently attacked as those

artificially nourished. Professor *Plum* points out that Danish children suffering from celiac disease are more frequently born during the winter than in summer time. That is not the case in our material.

Table 2.

<½ year .....	7	43 (58 per cent)
7th to 9th month ..	20	
10th to 12th month ..	16	
1 to 1½ years ....	16	
1½ to 2 years ....	10	
>2 years .....	5	

Table 2 presents the age when the disease started. In the literature on this subject it is usually said that the disease starts in the second year of life whereas our material shows that the first symptoms appear in the second half of the first year in half of the cases. In 7 cases the disease started before that time.

*Symptomatology.* The preponderant symptoms in the incipient stage were a gradually developing anorexia and vomiting accompanied by some occasional looseness of bowels. Later on cessation in the increase, and even loss in weight, periods of ill-smelling, foaming stools, remarkably big stomach, and bad temper were observed. In the serious cases the general state of health was greatly reduced with dystrophy and emaciation. In 11 patients the disease started in connection with acute infections in the upper respiratory tract, or with one of the usual infectious child diseases. In 18 patients it even started as an acute enteritis with or without fever. Not infrequently the first manifestation occurred at the time of changing from fluid to solid food.

32 children were suffering from hypochromic anemia (43 per cent). Hyperchromic or megalocytic anemia occasionally described in celiac disease, was not seen in our material. Most of the children had a slight anemia, only 4 patients had a percentage of hemoglobin lower than 50. The index was low, ranging from 0.5 to 0.8. The number of reticulocytes was

low, too. In 10 patients it varied between 0 and 9 per thousand, in one single case it was 13 per thousand.

Determinations of the serum iron have been made in 40 cases (Table 3). The values of the serum iron are very low, in 25 out of 40 children below 50 γ per cent. In the anemia

Table 3.

Serum iron in γ per cent:	Number of patients	Anemic patients
>100 .....	3	
71 to 100 .....	4	1
51 „ 70 .....	8	2
41 „ 50 .....	7	2
31 „ 40 .....	11	10
21 „ 30 .....	5	2
11 „ 20 .....	2	1

group alone, 15 out of 18 had figures below 50 γ pr. cent. Most of these patients, however, are to be found in the age group from  $\frac{1}{2}$  to 2 years, in which the values of the serum iron are normally lower than in adults. The low amount of serum iron in celiac patients is probably due to poor resorption of the iron in the food. The frequent infections certainly have some influence, too.

10 patients were suffering from rickets; 4 of these had tetany. Examination of the amount of blood phosphorus has been performed in 72 children (Table 4).

Table 4.

Anorganic blood phosphorus in mg. per cent:	Number of patients:	Number of patients with rickets:
<2.1 .....	9	6
2.1 to 3 .....	8	2
3.1 „ 4 .....	18	2
4.1 „ 4.5 .....	13	
>4.5 .....	24	

If 4 mg. per cent is set as a limit value for the normal amount of anorganic blood phosphorus, we see that one half of the cases of celiac disease have subnormal values. A far more frequent occurrence of rickets was therefore to be expected. We see here a confirmation of the old experience: No growth, no rickets. The majority of these patients show, as will be known, little or no increase in height during long periods.

9 patients were suffering from tetany, manifest or latent. The amount of serum calcium has been determined in all patients but one. Not only in tetany patients, but also in eleven others, reduced values were observed. X-ray pictures of the skeleton showed pronounced osteoporosis in 39 out of 69 children. 14 had slight osteoporosis in the skeleton, and in 16 X-ray examination revealed normal condition.

Scurvy was seen in 2 patients; in one of them this was also confirmed by X-ray pictures. Determinations of the amount of ascorbic acid in serum have been performed in 52. 75 per cent showed figures lower than 30 mg. per cent, and almost 50 per cent showed very low figures under 0,11 mg. per cent.

Hypoprothrombinemia was demonstrated in 21 children, and 3 of them suffered from manifest Kavitaminosis with cutaneous hemorrhages.

Reduced serum proteins with instability of the water balance (which among other signs appears in variable weight and edema), is of no rare occurrence in celiac disease. In 11 out of 41 patients the examination revealed reduced serum proteins. 7 were edematous.

A flat glucose tolerance curve is a very important aid in the diagnosis of celiac disease, and some investigators do not accept this diagnosis without such a flat curve. A. Ödegård who presented a closer analysis of this matter at the pediatric congress in Helsingfors in 1946, said in his conclusion that a flat curve speaks strongly in favour of the diagnosis of celiac disease, but he also added that a normally running curve does not exclude the diagnosis. The present material, which is a considerable augmentation of Ödegård's, fully confirms his conclusions. 84 per cent show an increase lower than

40 mg. per cent, and about 65 per cent below 30 mg. per cent. The aspect of the glucose tolerance test seems to some extent related to the phase of the disease. The worse the phase, the flatter the curve and vice versa.

Increased amount of fat in the stools is perhaps the most constant symptom in patients suffering from celiac disease, provided that they have received usual food beforehand. This has been examined in 60 patients, and in 55 of these the amount of fat was higher than normal (more than 25 per cent of dry feces). The five patients showing normal values had dietary treatment during a longer period.

X-ray examination of the intestinal tract has been made in 56 cases, and the pictures have been looked over by *O. Husebye* at the X-ray Department of Rikshospitalet. The following conditions were observed in most of them: 1) No picture, or only a dim one of the mucous membrane relief. 2) Cloggy or dotted distribution of the barium meal. 3) Dystonia of the intestines. No particular change in the time of passage was observed.

Folic acid has been tried in 8 patients without any effect.

Of the 74 children included in this material 3 died during their stay in the hospital. All of them were serious cases. In one case the post-mortem examination revealed a lipomatous pseudohyperplasia of the pancreas. Rachitic bones and bronchitis were observed in the second case, and in the third, a scattered and moderate fibrosis in the pancreas and a fatty degenerated liver were found. The two latter cases had both severe and prolonged attacks of tetany.

While 74 patients suffering from celiac disease have been treated in the hospital since the Jan. 1, 1940, we have in the same period made the diagnosis of pancreatic fibrosis in 4 cases.

Further details about the investigation to be published in "Nordisk Medicin".

From The Children's Clinic at the University, Helsinki.  
Head: Professor Arvo Ylppö.

## AN ATTEMPT TO DEVISE A GLUCOSE ABSORPTION TEST

By  
O. SOMERSALO (Finland).

*Author's abstract.*

The aim has been to devise a test which might indicate the rate of absorption of glucose from the gastro-intestinal tract. If a normal person be given glucose solution to drink and a glucose tolerance test be performed after the decrease of the blood sugar, the intravenous curve sinks more rapidly than if the person has not previously been drinking glucose. The glucose absorption has catalysed the utilisation of the glucose given intravenously in the same way as the perorally given sugar in the Staub-Traugott effect (Fig. 1). If the intravenous tolerance test be performed during the *period of resorption*, i. e., before the decrease of the blood sugar, this shortening of the curve is not seen, or there may even be a lengthening of the curve. The shortening of the intravenous curve, which can be expressed in minutes, then shows the *degree* of the catalysis caused by the absorption of glucose. This catalysis depends

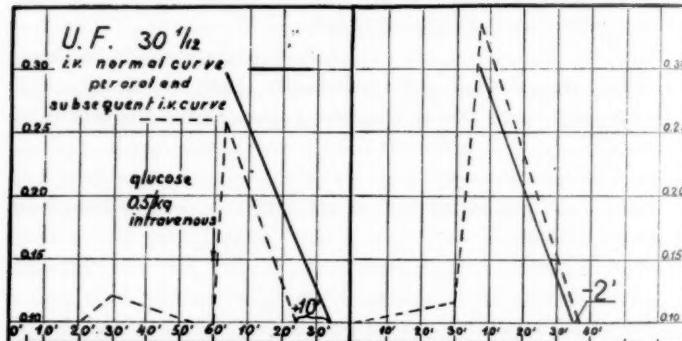


Fig. 1.

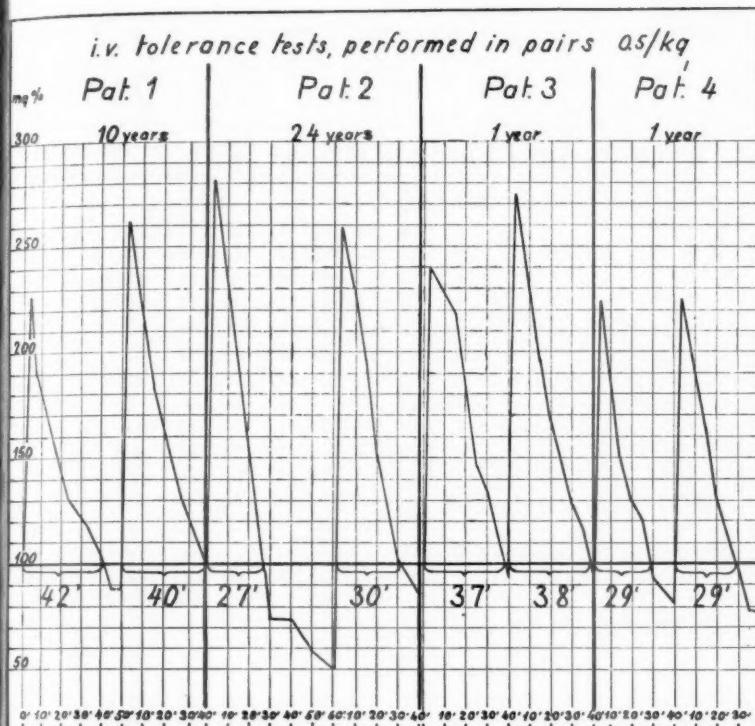


Fig. 2.

probably not solely on the increase of blood sugar, since a foregoing intravenous tolerance test where the blood sugar reaches much higher values — up to 200-300 mg. % — usually does not shorten the following intravenous blood sugar curve to such an extent. (Fig. 2).

Table 1 shows those cases in which the shortening of the intravenous curve is obvious. It was found that this group consisted of all my healthy test cases as well as one patient with celiac disease, who is convalescent and has a normal percentage of fat in the feces. It is to be noted that the test is positive (i. e., a shortening of the intravenous curve is found)

Table 1.

Name	Age	Diagnosis	Weight	Date	Length of intravenous curve in minutes 0.5 g glucose/kg a	The peroral curve	Fasting value mg % Max.	Time from peroral to intravenous administration (min)	Last value of peroral curve	Length of next intravenous curve in minutes b	a - b
U. F. 30	frisk		65.0	26.3	34	—	—	—	—	—	—
			29.4	—	90	12	150	104	26	+ 8	
			2.5	—	88	120	60	94	24	+ 10	
			5.5	—	95	125	45	117	27	+ 7	
			9.5	—	81	116	30	116	36	- 2	
			29.5	—	89	118	60	105	27	+ 7	
E. K. 29 $\frac{1}{2}$	»		59.0	15.1	—	86	148	60	142	58	+ 7
			19.1	—	76	147	120	79	19	+ 46	
K. O. 27	»		58.0	28.3	53	—	—	—	—	—	—
			30.3	—	88	117	150	85	36	+ 17	
			16.5	—	86	136	120	98	46	+ 7	
			19.5	—	97	124	90	109	40	+ 13	
R. M. 11	»		29.0	8.3	—	89	153	60	101	42	+ 12
			9.3	54	—	—	—	—	—	—	—
L. P. 7 $\frac{2}{12}$	»		22.2	27.7	47	—	—	—	—	—	—
			28.7	—	94	155	60	155	>60	—	—
			30.7	—	90	133	140	97	17	+ 30	
J. K. 1 $\frac{11}{12}$	Conv.p. coeliac.		11.9	24.12	37	—	—	—	—	—	—
			16.1	40	—	—	—	—	—	—	—
			17.1	35	—	—	—	—	—	—	—
			11.2	—	96	134	90	102	19	+ 16	
M. K. 3 $\frac{1}{12}$	Furunc.		6.6	5.8	—	86	108	90	93	21	—
			7.8	36	—	—	—	—	—	+ 15	

Table 2.

A. H. 3 $\frac{1}{12}$	Coeliaki	13.1	26.4	41	—	—	—	—	—	—	—
				4.5	—	80	95	45	93	36	+ 5
A. H. 4 $\frac{1}{12}$	»	13.6	3.5	34	—	—	—	—	—	—	—
				15.5	—	77	123	60	123	36	- 2
P. H. 3 $\frac{4}{12}$	»	6.6	19.12	36	—	—	—	—	—	—	—
				3.6	47	—	—	—	—	—	—
				28.7	36	—	—	—	—	—	—
				3.6	29.7	—	77	97	60	97	36
L. H. 3 $\frac{4}{12}$	»	7.2	17.3	47	—	—	—	—	—	—	—
				11.12	41	—	—	—	—	—	—
				9.1	33	—	—	—	—	—	—



Table 3.

Name	Age	Diagnosis	Weight	Date	Length of intravenous curve in minutes, 0.5 g glucose/kg	The peroral curve	Fasting value mg % Max.	Time from peroral to intravenous administration (min)	Last value of peroral curve	Length of next intravenous curve in minutes	(n = 1)
		Coeliaki	16.2	—	69 134	60 134	>60	>—	23		P.
			17.2	—	77 130	70 92	—	—	18		M.
			24.2	—	84 165	70 158	>60	>—	23		M.
M. S.	2 5/12	*	9.1	17.4	— 87 92	60 85	60	— 19			L.
				26.4	41	—	—	—	—		L.
R. R.	2 11/12	*	9.2	23.4	42	—	—	—	—		P.
				31.4	—	— 120	84	59	— 17		L.
				31.5	—	— 120	89	52	— 10		E.
			10.6 10.8	36	—	—	—	—	—		R.
L. H.	6 10/12	*	17.3	25.2	52	—	—	—	—		K.
				10.4	61	—	—	—	—		S.
				20.4	— 88 103	75 97	70	— 19			
			16.3	27.4	51	—	—	—	—		
				29.4	61	—	—	—	—		
				3.5	60	—	—	—	—		

also in the cases, U. F., K. O., and M. K., where the blood sugar in the peroral tolerance test does not increase much over 100 mg. %.

Table 2 shows such cases where there is no certain shortening nor lengthening of the subsequent intravenous curve. All these are celiac cases except for two sucklings.

Table 3 shows the cases where there is a distinct lengthening of the curve. All these are typical celiac cases.

Of these cases, then, all those with a lengthening of the intravenous curve are celiac cases. Those giving an uncertain result consist partly of celiac cases, partly of healthy sucklings. And those showing a shortening of the intravenous curve are all healthy. It is, however, obvious that this test must be further investigated, especially with regard to sucklings.

In order to determine to what extent a slow evacuation of the stomach is the cause of a low glucose tolerance curve in celiac disease, glucose solution has been passed into the duodenum through a duodenal catheter. The results are shown

Table 4.

Name	Age	Diagnosis	Weight	Date	Length of intravenous curve in minutes, 0.5 g glucose/kg	The duodenal curve	Fasting value mg % Max.	Time from duodenal to intravenous administration (min)	Last value of duodenal curve	Length of next intravenous curve in minutes	a - b
P. S.	6 2/12	Celiaki	15.6	27.7	—	99	150	—	—	—	—
				6.8	—	95	116	90	90	27	—
				7.8	28	—	—	—	—	—	+ 1
M. H.	1 6/12	»	6.5	16.6	—	99	125	—	—	—	—
M. J.	2 5/12	»	6.2	17.6	—	74	100	—	—	—	—
L. H.	6 10/12	»	17.3	24.5	—	98	180	—	—	—	—
L. H.	3 4/12	»	8.2	27.7	31	—	—	—	—	—	—
				2.8	—	71	103	90	103	21	+ 10
P. H.	3 4/12	»	8.6	28.7	36	—	—	—	—	—	—
				3.8	—	101	217	100	79	16	+ 20
L. H.	2 2/12	»	8.2	4.8	—	82	119	90	81	28	—
				11.8	26	—	—	—	—	—	2
E. N.	3	»	11.5	29.7	—	88	130	—	—	—	—
				6.8	36	—	—	—	—	—	—
				7.8	—	100	160	90	97	27	+ 9
R. R.	2 11/12	»	10.6	28.7	—	94	204	—	—	—	—
				10.8	36	—	—	—	—	—	—
				11.8	—	90	125	90	94	45	— 9
K. A.	1	»	6.5	30.7	35	—	—	—	—	—	—
				10.8	—	76	77	105	76	37	— 2
S. N.	11/12	Imbecill.	7.5	5.8	33	—	—	—	—	—	—
				10.8	—	82	209	80	72	19	+ 14

in Table 4. In some patients normal or hypernormal rises are found, in others low curves. On seven patients a combined duodenal-intravenous tolerance test has been performed; three of them show a distinct positive result, i. e., the subsequent intravenous curve is shortened.

As a result it can be said that the combined peroral-intravenous glucose tolerance test may be of some use when estimating the rate of absorption. However, it is probable that the duodenal-intravenous test, which eliminates the influence of the stomach, is more reliable when estimating absorption from the intestine.

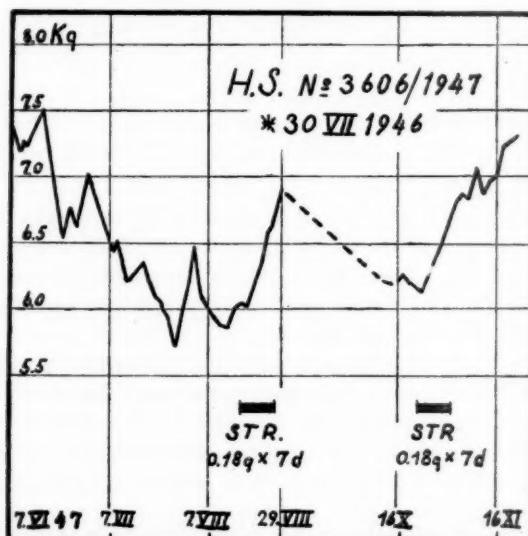
## DISCUSSION

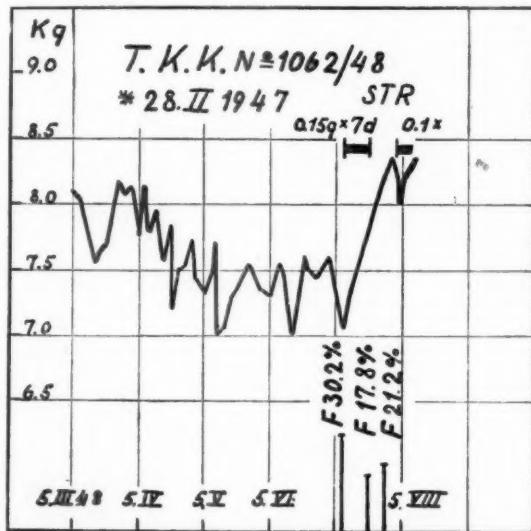
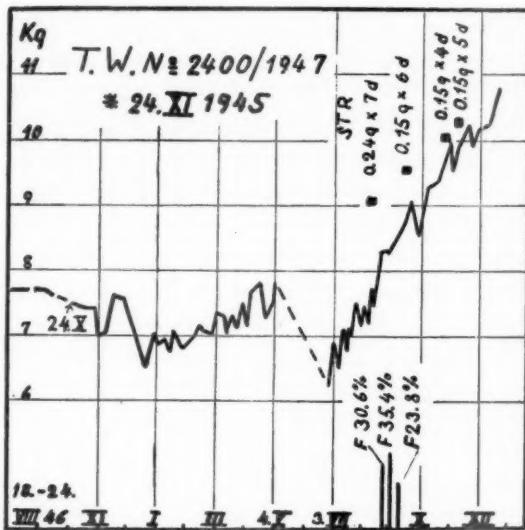
*C. E. Räihä (Finland).*

I wish to show some weight curves for patients with celiac disease, who have been treated with streptomycin by mouth.

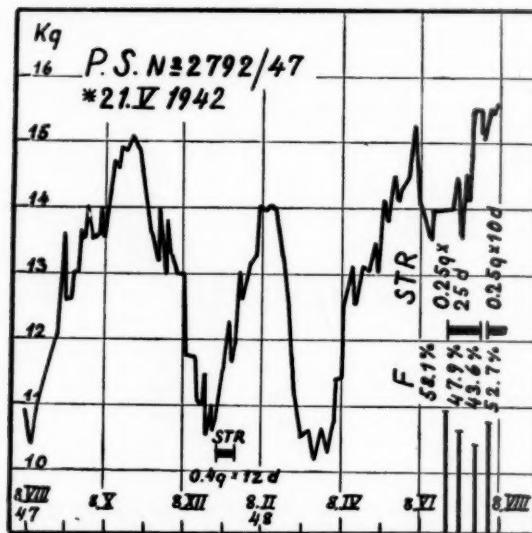
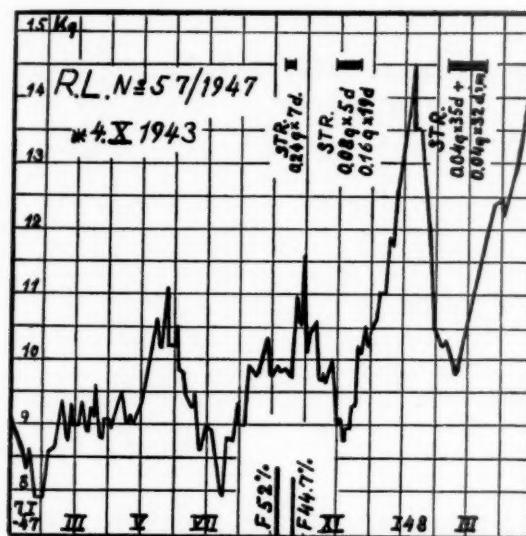
This treatment is based on the following considerations:

The disease does not occur in breast-fed children, but often it appears in connection with the change from mother's milk to artificial feeding. It also appears frequently in connection with dyspepsia. Duodenal contents withdrawn with a tube show often an abundant bacterial flora. It may be that some change in the bacterial flora of the intestine or spreading of the flora upwards to sections of the gut which should be free from bacteria, plays a rôle in the etiology of the disease. It has been our impression that in our cases of summer gastro-enteritis with severe toxic complication a favorable effect may be obtained with streptomycin; and we know that by means of streptomycin we are able in a high degree to reduce the amount of colibacteria and streptococci in the intestines. We see that under streptomycin therapy the stools become more firm in consistency, less voluminous, with reduction of their fat content. At the same time we obtained a gain in weight. In the younger patients this improvement seems more lasting, while





## Section II



in the older patients it is more difficult to obtain such a result, and here the effect is more transitory.

I fully realize that celiac disease is very capricious, and that a favorable therapeutic result does not allow of far-reaching conclusions. Still, I think that the weight curves here presented will justify further study of this problem.

Finally, of the 6 cases which Professor Plum has treated with streptomycin, 3 show a similar positive result.

#### B. Kromann (Denmark).

With reference to Dr. Räihä's paper I wish to point out that by means of a combined penicillin-streptomycin therapy it is practicable even to render the intestinal content perfectly sterile for a short time.

In Queen Louise's Children's Hospital we recently have treated a 12-year-old boy who had been suffering from hemorrhagic colitis since he was 6 years old.

He is allergic, with pronounced idiosyncasy to cow's milk. With the idea that perhaps he also had developed idiosyncasy to his particular intestinal bacteria we attempted to provide him with a new intestinal flora.

Cultures from the feces prior to the treatment yielded a) innumerable lactose fermenting colonies of Gram-negative rods, and b) numerous colonies of Gram-positive cocci.

The Gram-negative rods were moderately sensitive to streptomycin.

The Gram-positive cocci were moderately sensitive to streptomycin and penicillin.

After 4 days treatment with streptomycin perorally (200 mg  $\times$  4) and by injection (250 mg  $\times$  4) cultures from the stools showed innumerable streptococcus-like colonies of Gram-positive rods. These bacteria were resistant to streptomycin but sensitive to penicillin.

Now, therefore, the boy was given 80,000 I. U. penicillin  $\times$  4 for 3 days by injection, and then both streptomycin and penicillin in the dosage mentioned for 4 days.

*After the combined treatment with penicillin + streptomycin cultures from the stool showed no growth on Conradi-Drigalski agar as well as on ordinary blood agar.*

#### C. Dueholm (Denmark).

As shown at the congressional exhibition by Henning Andersen and Dueholm, in 18 children suffering from celiac disease, enzymatic

analyses on the duodenal juice have shown a decrease in the lipase activity to about the level of the lower limit in normal children. This moderate decrease may not be assumed to result in digestive insufficiency.

With regard to the report by Dr. Räihä concerning the result obtained from treatment of celiac disease with streptomycin by mouth it may be mentioned that the duodenal juice withdrawn from patients with celiac disease most often was sterile, and that the bacterial growth obtained by cultivation in certain cases showed no uniformity (contamination).

*E. Mannheimer (Sweden).*

With regard to the great toxicity of streptomycin I should like to ask whether Dr. Räihä and Dr. Kromann in their cases found any symptoms of toxic by-effects. Previously streptomycin medication has been employed primarily on vital indication. So caution has to be exercised at its employment in chronic cases.

*C. E. Räihä (Finland).*

In reply to Dr. Mannheimer's question I wish to emphasize that the amounts of streptomycin here employed are small, and that the remedy is given by mouth.

*A. Wallgren (Sweden).*

I wish to call attention to the remarkably uneven geographical occurrence of celiac disease in the Scandinavian countries. From the account given by Dr. Tho it is evident that the disease is of increasing frequency in Norway. It is common also in Finland and Denmark, whereas in Sweden it is relatively rare. Dr. Tho stated that within the same period as he had had 4 cases of pancreatic fibrosis he had seen 20 cases of celiac disease. In the Norrtull Clinic, within the last twelve months, per same number of cases of pancreatic fibrosis we have seen only one new case of celiac disease. This uneven distribution of celiac disease has previously been interpreted as evidence that the disease would be due to an insufficient diet: only a few cases in Sweden which was largely spared in the war, numerous cases in the other Scandinavian countries that were affected by the war.

Now, however, the frequency of celiac disease is increasing in Norway, and it still remains high in Denmark and Finland in spite of the fact that dietary conditions practically are the same in all

the Scandinavian countries. So, now, the afore-mentioned etiological theory may hardly be maintained.

The successful therapeutic experiments with streptomycin mentioned by Dr. Räihä may suggest a possible bacterial pathogenesis of the syndrome. It may be that a streptomycin-sensitive agent in these cases has been responsible for the celiac symptoms and that this hypothetical agent is less wide-spread in Sweden than in the other Scandinavian countries.



### **SECTION III**

**SUNDAY, AUGUST 15.**

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*From The Children's Clinic at the University, Helsinki.  
Head: Professor Arvo Ylppö.*

**STUDIES ON THE CEREBROSPINAL FLUID IN  
PREMATURE INFANTS\*)**

By  
**E. OTILA (Finland).**  
*Author's abstract.*

Besides an increase in the cell count and in the protein content, the cerebrospinal fluid in newborn premature infants given very often a positive tryptophan reaction. Together with certain other properties of the fluid in premature infants, this observation indicates that its protein content in some way differs qualitatively from the protein content of normal cerebrospinal fluid. In premature infants a very high degree of meningeal permeability can be demonstrated by intravenous injection of uranin.

*P. Plum (Denmark).*

I should like to know whether experimental examination of the cerebrospinal fluid in the fetus might offer any explanation of the high protein content of the fluid in the newborn.

*Arvo Ylppö (Finland).*

After Dr. Otila's studies it is easy to understand why serous or other forms of meningitis are so common in septic infections in premature infants.

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\*) Has been published in *Acta Paediatrica*, vol. XXXV, Suppl. VIII, 1948.

SUR LES ISOAGGLUTININES ET LES ISOLYSINES  
CHEZ LES PRÉMATURÉS\*)

de  
AINO YLIRUOKANEN (Helsinki, Finlande).  
*extrait d'auteur.*

Des isoagglutinines sont formées chez les enfants nés à terme en grande quantité déjà au 4ème mois et ces enfants ont déjà presque toutes leurs isoagglutinines à l'âge de six mois. Les isolysines sont formées plus tard. La capacité de produire ces substances est plus faible chez les prématurés. Dans les cas étudiés ici on a pu constater chez des prématurés âgés de 6-7 mois des isoagglutinines seulement en 50 % des cas et des isolysines dans quelques cas rares. La capacité de formation des anticorps était dans certain cas en proportion directe avec la prématurité.

DISCUSSION

*Arvo Ylppö (Finland).*

The studies reported by Dr. Yliruokanen show that in premature children we have to reckon with complications arising from injection of blood that does not belong to the suitable blood group. Hitherto, generally, no particular attention has been paid to which group the blood belonged to that was injected into young premature infants.

\*) Sera publié plus tard in extenso dans *Acta Pædiatr.*

*From the Children's Hospital, Martinsvej, Copenhagen.  
Head: A. Rothe-Meyer, M. D.*

## HIGH PROTEIN NUTRITION IN PREMATURES\*)

By  
**ARNE ROTHE-MEYER (Denmark).**

*Author's abstract.*

The benefit of high protein nutrition in prematures has been demonstrated in two ways. *Levine & Gordon* in their work on acidified cow's milk mixtures that were reduced in fat and high in protein concluded that this diet was advantageous and should be preferred to human milk. By supplementing mother's milk with an amino acid-glycose mixture *Magnusson* obtained a remarkably increased weight-gain in prematures during their first month of life.

Nutrition experiments along both these lines have been carried out at the Children's Hospital, Martinsvej, Copenhagen, during the past two years. In a preliminary report — read at the International Conference of Physicians in London in September 1947 — a series of prematures fed on human milk supplemented with amino acid (up to a daily total protein intake of 5 gr. per kg.) showed no increased weight as compared with a series fed solely on human milk. This result may have been due to inefficiency of the Danish hydrolysate aminolin, an acid digest. In recent experiments a new enzymatic digest (amino-acid Wanderer) has been used; but the number of cases is yet too small to draw any conclusions (see Fig. 1).

On comparing the daily weight-gain from the 14' to the 42' day of life in prematures fed on human milk with those fed on undiluted half-skimmed citric acid milk (Fig. 1) a greater weight-increase for the group fed on cow's milk mixture has been found, the difference (33 against 26 gr.) being statistically significant.

\*) To be published in extenso elsewhere.

These findings tend to confirm Levine's thesis of the preferability of certain cow's milk mixtures to human milk. But before accepting this rather startling statement — hitherto based solely upon the criterion of weight-gain — it is necessary to look for possible disadvantages in this kind of nutrition for prematures.

1948

	birth weight	number of cases	weight gain 14'-42' day
<b>Human milk + amino acid</b>	< 2000	5	25
	> 2000	4	35
<b>Human milk</b>		9	29 g
	< 2000	23	25
	> 2000	18	28
<b>Allaitement mixte</b>		41	26 g
	< 2000	6	26
	> 2000	12	31
<b>½ skimmed citric acid milk</b>		18	29 g
	< 2000	9	30
	> 2000	20	34
		29	33 g

Fig. 1.

A tendency towards acidosis in prematures fed on high protein diet has been demonstrated by *Darrow*. Investigations of the bicarbonate levels in our series will be read at this congress by Dr. Dupont.

Determination of the *blood urea* levels in our prematures showed some interesting facts. The values in prematures fed solely on human milk during the first two weeks of life varied between 5 mg. % and 40 mg. %. This great variation probably is due to the functional immaturity and tendency to dehydration during the neonatal period. However, at the age of four

weeks the great majority of urea values is found within the limits of 5 mg. % to 15 mg. %.

The values in prematures fed on half-skimmed citric acid milk starts with a similar large variation on a somewhat higher level (10 mg. % - 40 mg. %). But unlike the human milk prematures, the cow's milk babies continue on this higher level (20 mg. % - 40 mg. %) even at, and after, the age of four weeks, not infrequently touching still higher levels.

Thus it seems safe to conclude that blood urea in prematures fed on half-skimmed citric acid milk attain levels that are much higher than those of prematures fed on human milk, and that such high levels cannot but represent increased functional strain.

*From The Children's Hospital, Martinsvej, Copenhagen.  
Head: A. Rothe-Meyer, M.D.*

**ON BLOOD-AMINO-ACID LEVELS IN PREMATURES  
AND INFANTS\*)**

By  
**HARALD KREUTZFELDT** (Denmark).  
*Author's abstract.*

Investigations of amino-acid values in 48 prematures and infants 1-50 days old have shown that the fasting level is somewhat higher than in adults, namely 7.92 - 7.78 - and 7.81 mg % in 3 groups weighing 1500-2000 g., 2000-3000 g., and 3000-4000 g., respectively. The fasting level was equal in 3 groups which were given: 1) human milk, 2) human milk + amino-acid, and 3) half-skimmed acidified milk. — The rise 1 hour after the meal for these 3 groups was 4.38, 14.95, and 13.86 %, respectively, that is, consistently higher in the diets rich in protein than in human milk alone.

In 10 healthy children between 6 and 10 years old the fasting level was 6.33 mg. %, — that is, the same as in adults.

\*) To be published in extenso elsewhere.

*From The Children's Hospital, Martinsvej, Copenhagen.*

*Head: A. Rothe-Meyer, M. D.*

*and The Children's Hospital, Fuglebakken, Copenhagen.*

*Head: V. Poulsen, M. D.*

## INVESTIGATIONS ON SERUM BICARBONATE IN PREMATURES\*)

By

ANNALISE DUPONT (Denmark).

*Author's abstract.*

### *Methods.*

The micromethod, applying van Slyke's manometrial apparatus. The blood investigated was taken either from the heel or from the fontanel.

In the fontanel blood the bicarbonate value is higher than in the heel blood (2.6 mmol). (This was found by comparing two groups of prematures under the same conditions.)

### *Normal Values.*

No relation was found between the bicarbonate values and the birth weight nor the actual weight. During the first two weeks a greater dispersion of the bicarbonate values was found than later on.

By examining the fontanel blood it was found that the average bicarbonate values of 46 healthy prematures fed on human milk was 22.75 millimol.

Among 31 prematures fed on half-skimmed citric acid milk it was 18.97 millimol. Prematures fed on half-skimmed citric acid milk have a significantly lower bicarbonate value than those fed on human milk.

No significant difference in the average bicarbonate values was found by examining heel blood among two groups of pre-

\*) To be published in extenso elsewhere.

matures, one fed on human milk, the other on allaitement mixte (human milk and cow's milk mixtures).

*Tendency to Acidosis in Pathological Conditions.*

Prematures with slight upper respiratory infections have normal bicarbonate values. On the other hand, prematures drinking unwillingly and thriving poorly frequently show low bicarbonate values, i.e., that even vague symptoms of imminent indigestion without diarrhoea and vomiting are indications for the examination of the bicarbonate value of the serum.

From The Children's Hospital, Martinsvej, Copenhagen.  
Head: A. Rothe-Meyer, M.D.

## BLOOD SUGAR IN PREMATURES\*)

By  
FOLKE TUDVAD (Denmark).

*Author's abstract.*

The fasting blood sugar in 38 prematures within the age period of 0-28 days has been determined at the Children's Hospital, Martinsvej, Copenhagen. Beginning three hours after a meal the blood sugar has been measured every 30 minutes for three hours. Altogether 103 estimations with 552 single determinations have been made.

The fasting level was found between 45 and 70 mg. per cent, independent of the age, birth weight and actual weight of the premature baby. There was, however, great variation, and 27 per cent of the single determinations were under 50 mg. per cent.

The renal threshold for glucose has been determined with the method of Bjering and Iversen in which the glucose tolerance curve is carried out using subcutaneous injection or intravenous drip of glucose. The filtration rate is determined through inulin clearance. The urine volume and the urine contents of sugar having been determined, the reabsorbed quantity of glucose may be found and recorded as a curve in a coordinating system against the blood sugar. In this system the intersectional points between the curve and the previously established line of balance indicates the renal threshold. (Fig. 1.)

The renal threshold of 8 prematures was found between 139 and 190 mg. per cent for increasing blood sugar and between 104 and 163 mg. per cent for decreasing blood sugar.

The alimentary rise of blood sugar in 27 prematures fed on

\*) To be published in extenso elsewhere.

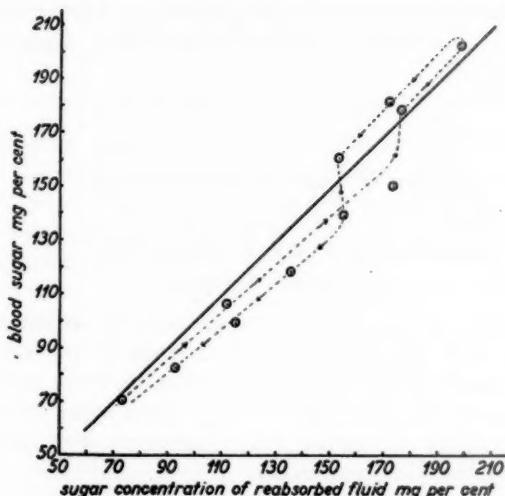


Fig. 1. Estimation of renal threshold for glucose

human milk (maximum 2.5 g. carbohydrate per kilogram body weight) did not exceed 130 mg. per cent. In 23 prematures fed on cow's milk mixtures (maximum 3.2 g. carbohydrate per kilogram body weight) an alimentary increase above 140 mg. per cent was found four times. After oral glucose administration (maximum 2.8 g. per kilogram body weight) to 22 prematures, only one level exceeded 140 mg. per cent.

In conclusion it may be said that alimentary glycosuria occurs extremely seldom in prematures fed on human milk or ordinary cow's milk mixtures, whereas parenteral administration of or above 1.5 g. of glucose per kilogram body weight always causes glycosuria.

#### DISCUSSION

J. Henning Magnusson (Sweden).

Accounts of oral treatment of prematures with casein hydrolysate have been published by many authors. The results vary with the preparations employed, which is quite natural. For, as far as pro-

tein hydrolysate is concerned, the matter is very confused, and we have not as yet attained any uniform standardization. Personally, I am quite convinced that we must insist on a very high standard of any preparation for prematures. As regards the purity of the preparations, it must be on a level with that of hydrolysate for intravenous injection.

Such a preparation should be produced through hydrolysis of casein with pure enzymes. The hydrolytic product should be dialyzed. Dialysis yields a mixture of amino acids which on oral administration has no toxic effect on the gastro-intestinal tract. Otherwise, such toxic effects — usually manifested in the form of diarrhoea — may become so intense that the organism is unable to utilize the nutrition supplied and there will be a loss of weight. The dialysis separates the high molecular protein components that may give rise to anaphylactic and allergic reactions. In animal experiments anaphylaxis may be produced with non-dialyzed casein hydrolysate whereas the dialyzable part of the hydrolysate is free from the anaphylaxis-producing substances. Finally, the split quotient — i. e., the ratio  $\frac{\text{amino acid N}}{\text{total N}}$  — must be sufficiently

high. In the preparation employed by me, Aminosol, this quotient has averaged 0.56.

Quite recently the Council on Pharmacy and Chemistry, U.S.A., has published the requirements for protein hydrolysate to be entered in the 1948 edition of New and Nonofficial Remedies. According to these requirements only preparations with a split quotient over 0.50 may be designated as hydrolysates.

Using hydrolysate fulfilling these criteria, many authors have obtained good results from the oral administration of the preparation to prematures in addition to breast milk.

In the English pharmacological literature it appears as if a split quotient as low as 0.20 is considered sufficient for oral preparations, and 0.30 for intravenous ones. According to the requirements above such preparations must not be designated as hydrolysates. In 1946 I had occasion to try two preparations of that kind. One gave untoward reactions from the intestinal tract in the form of diarrhoea and standstill of the body-weight, and the other preparation had no demonstrable effect.

In the beginning of this year I had occasion to try a somewhat similar preparation with a split quotient of 0.27 to 0.29. It is the same preparation that was used in the studies reported here. According to the forementioned requirements, this preparation must not either be designated as hydrolysate, and I also failed to obtain any positively demonstrable results with this preparation.

*P. Plum* (Denmark).

I wish to congratulate Dr. Rothe-Meyer and his collaborators to the thorough studies they have reported, increasing our knowledge in this field.

I should like to ask whether a casein preparation — as, for instance, the Danish "seccosan" — gives just as good results as amino acid preparations. Further, whether the children with high blood urea values show any abnormality in the urine, possibly an increase of the normal proteinuria.

*L. Salomonsen* (Norway).

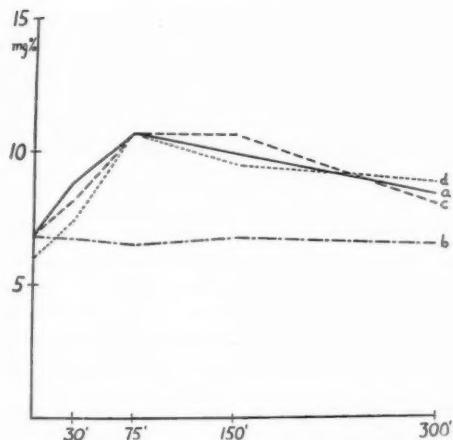
It may be appropriate to emphasize that we are not to look upon the *increase in the weight* of prematures as the only criterion of their thriving. It is a very risky matter in the nutrition of these infants to replace mother's milk with an artificial diet as for instance half-skimmed citric acid milk merely because this diet gives a greater gain in weight. It is the general thriving of the children, their morbidity and mortality which are decisive when we are to estimate the value of their nutrition.

*Lennart Hesselvik* (Sweden).

In the Norrtull Clinic, in the past year, we have carried out a number of analyses of the amino acid content of the blood in infants, employing a method given by Krauel (J. Lab. & Clin. Med. 29:222, 1944), which is easy to carry out and sufficiently accurate for practical use.

Like other investigators, we found the fasting values to vary within rather wide limits (for our normal material, so far, between 3.7 and 9.9 mg. % amino-acid N, with an average of 7.3 mg. %) without any distinct connection with the age of the child. Our interest, however, has been aimed in particular on the course of the amino-acid curve after ingestion of protein. Largely we have employed the same technique as West, Wilson & Eyles (Am. J. Dis. Child. 72: 251, 1946), giving the infants an amount of gelatin corresponding to 1.22 g. pure albumen dissolved in 30 ml. water per kg. of body weight. The typical form of the curve obtained in this way in a normal infant is shown in the Fig. (curve a). In most of the diseases in which we have examined the appearance of this curve it has not shown any distinct difference. Like the authors just mentioned, however, we have found that infants with *cystic fibrosis of the pancreas* may show a perfectly flat curve (curve b), corresponding to the decreased amino-acid absorption.

In contrast to the authors mentioned, however, we have observed



three cases of unquestionable cystic fibrosis of the pancreas in which the form of this curve has been altogether normal (curves c and d are from two of these cases). Naturally this detracts from the diagnostic value of the method. Still, the method is of importance, for instance to an estimation of the possibilities of the substitution therapy in certain cases of cystic fibrosis of the pancreas.

*A. Lichtenstein (Sweden):*

I agree with Prof. Salomonsen that the value of a nutritional method must not be estimated only on the basis of the gain in weight. Dr. Rothe-Meyer, however, has explicitly emphasized that the weight-gain must not be the only criterion in a comparison between mother's milk and cow's milk.

*Carl Friderichsen (Denmark)*

To Dr. Rothe-Meyer: We use half-skimmed milk with addition of lactic acid, and we have found the same good results with regard to weight-increase as you have obtained with citric acid.

As the immunity indeed is of the greatest importance, I wish to ask if from your material you can see whether the tendency to infection has been greater in the premature infants given artificial diet?

At present we are looking into the weight-increase and tendency to infection when mother's milk is given at the same time as half-

skimmed acid milk — as an allaitement mixte. This, I think, will be our future way of treatment.

To Dr. Dupont: Your studies confirm and explain very well the results I arrived at previously: that the acidosis in dyspepsia and intoxication appears the more rapidly and more severely the younger the child is, and that it is most pronounced in the prematures.

*Bo Vahlquist (Sweden).*

Just a few comments on the most interesting results presented. Dr. Kreutzfeldt showed figures demonstrating a more pronounced rise of the amino-acid concentration of the blood after skimmed citrido milk and casein hydrolysate as compared with human milk. It should be noted perhaps that such figures always represent a balance between absorption from the intestinal tract and outflow into the tissues. Differences in this latter factor might simulate greater differences in absorption than are actually present. The differences observed by Dr. Dupont in the bicarbonate concentration of blood taken by skin prick and by puncture of a vein is interesting. In corpuscular elements such as the erythrocytes a difference has previously been observed during the first week of life. I should like to know if these observations might be relevant for the differences in bicarbonate content or if differences in the oxygen contents of blood from the skin and blood from the vein might play a rôle.

*A. Ylppö (Finland).*

The first four papers form a sort of praise of mother's milk in the dietetic treatment of prematures. Various mixtures of cow's milk, indeed, will more readily give rise to excessively high blood sugar and nitrogen values and the CO<sub>2</sub> content of the blood will become too low. All these phenomena are unfavorable signs for which the initially somewhat greater increase in weight is no sufficient or desirable substitute.

*A. Rothe-Meyer (Denmark).*

I wish to thank Dr. Magnusson for the given information about the low split quotient of aminolin, which confirms our experiences. Has Dr. Magnusson carried out any studies of administration of aminosol *without* any addition of glucose?

To Professor Plum I can merely say that we have no experiences with seccosan. Systematic analyses of the urine have been omitted because we would not like to catheterize the prematures.

I quite agree with the points of view advanced by Professor Salomonsen concerning the criteria for clinical estimation of prematures. But when definite forms of diet are emphasized by authorities as being superior it will be justified and also necessary to deliberate pro et contra.

To Dr. Friderichsen I have to admit that my material is still all too small for any statements about resistance to infection.

*J. Henning Magnusson (Sweden).*

To the question whether I have used casein hydrolysate without any addition of glucose and about its dosage I can give the following information:

In order to make the experimental conditions as clearcut as

*Table 1.*

Case No.	Weight at birth	Day of life when the exp. began	Gain in weight (in grams)			
			Experimental periods			
			1 Mother's milk + aminosol	2 Mother's milk	3 Mother's milk + aminosol	4 Mother's milk
1	1410	11	210	80	250	110
2	1490	9	150	110	200	100
3	1500	9	190	30	210	60
4	1500	7	240	70	190	60
5	1430	9	110	20	140	90
6	1320	11	160	50	230	60
7	1640	10	180	20	220	60
8	1850	8	230	60	180	40
9	1760	10	90	120	270	130
10	1660	8	140	70	190	50
11	1490	10	170	80	250	40
12	1500	15	120	10	150	80

possible, in all the comparative studies carried out during the past two years I have used only casein hydrolysate (Aminosol). A dosage of about 2 g. per kg. of body weight daily has proved most suitable.

The following two tables illustrate the results. Both series consisted of prematures free from infection, with a low birth weight. All the experimental periods covered six days. In the individual cases the caloric supply was precisely the same in all four experimental periods.

In Table 1, a comparison is made between Aminosol and an

Table 2.

Case No.	Weight at birth	Day of life when the exp. began	Gain in weight (in grams)			
			Experimental periods			
			1 Mother's milk + casein	2 Mother's milk + aminosol	3 Mother's milk + casein	4 Mother's milk + aminosol
1 .....	1470	10	100	220	70	130
2 .....	1500	9	90	200	60	270
3 .....	1400	12	120	220	150	180
4 .....	1340	12	80	160	20	130
5 .....	1350	12	110	190	80	230
			Mother's milk + aminosol	Mother's milk + casein	Mother's milk + aminosol	Mother's milk + casein
6 .....	1480	9	130	70	140	100
7 .....	1410	10	270	120	240	150
8 .....	1390	11	240	125	290	50
9 .....	1510	9	140	70	110	120
10 .....	1500	10	170	120	270	80

equicaloric amount of breast milk; in Table 2 an equicaloric amount of native casein. The differences demonstrated here, which are directly evident from the two tabulations, are statistically significant.

*H. Kreutzfeldt (Denmark).*

To Dr. Vahlquist I have to admit that it would have been desirable for us to follow the absorption curve for aminolin with frequent determinations, but this has not yet been practicable.

*A. Dupont (Denmark).*

To Dr. Vahlquist I merely wish to say that I have found this difference between Fontanel blood and heel blood not only by comparing the average of two groups. Also in 20 infants from whom 2 samples of blood were taken simultaneously from the different places, the Fontanel values constantly were found to be higher than the others.

*From Sachsska Barnsjukhuset, Stockholm.  
Head: Docent H. Magnusson, M. D.*

THE DEVELOPMENT OF PEPSIN AND PANCREAS  
PROTEINASE IN PREMATURE AS COMPARED WITH  
FULL-TERM INFANTS\*)

By  
BIRGITTA WERNER (Sweden).  
*Author's abstract.*

The secretion pictures in the gastric mucous membrane and the pancreas have been examined with regard to pepsin in 70 cases, of which 41 were premature and with regard to trypsin in 41 cases, of which 30 were premature. The histological findings have been controlled in a number of the cases by chemical determination of the enzyme content. The material shows that the proteolytic enzyme system achieves a full-term capacity so late in fetal life that the premature infant must be considerably handicapped in comparison with the full-term infant in this respect, too, and to a greater extent than can be assumed from the degree of debility.

\*) To be published in extenso in *Acta paed. suppl. 6 vol. XXXV.*

*From the Pediatric Clinic at the Akademiska Sjukhuset, Uppsala,  
Head: Professor Curt Gyllenswärd.*

## **STUDIES ON CARBONIC ANHYDRASE IN PREMATURE INFANTS\*)**

By  
**RAGNAR BERFENSTAM (Sweden).**

*Author's abstract.*

Carbonic anhydrase is an enzyme which is necessary for the rapid disaggregation of  $H_2CO_3$  and  $H_2O$ . It is present in large amounts in the erythrocytes of adults and also in some other tissues. In 1942 Stevenson showed that the prematures have a low carbonic anhydrase level and he is of opinion that the cyanosis and bad condition of these infants might depend on this fact. Following blood transfusion he saw clinical improvement. The writer investigated the level of carbonic anhydrase in adults, newborn infants and prematures, and he demonstrated that 39 of 54 prematures on some occasion in the first days of life have about 5 % of the adult level, the average value for the normal newborn being about 50 % of that of the adults.

After an initial decrease in the first days of life, parallel to the fall in the hematocrite value, there is a slow spontaneous increase in the carbonic anhydrase level, yet the prematures do not reach the level of the normal newborn until several months after term.

An experimental increase in the enzyme level is obtained not only by blood transfusions but also by intramuscular blood injections. The supposition of the author that this fact is due to a resorption of undamaged blood corpuscles was confirmed by giving intramuscular injections of blood from an elliptocyte carrier to prematures: a large number of these

\*) To be published in extenso elsewhere.

corpuscles could be recognized in the circulating blood of the baby.

The author supports the findings of Stevenson, that the carbonic anhydrase is markedly low in prematures (1/20 of the adult level) and is also of the opinion that this fact may be of importance concerning the intermediary respiration. It is proposed to give blood injections to these patients in addition to all other therapeutical measures.

## THE EARLY PROGNOSIS FOR PREMATURES WITH DIFFERENT FORMS OF CARE

By

INGVAR ALM (Stockholm, Sweden).

*Author's abstract.*

An account is given of the mortality in the first year of life among children with a birth weight  $\leq 2500$  g. and a birth length of  $\leq 35$  cm., who in the following will be designated as prematures. The material was collected from the following maternity hospitals:

*ABBH* is a separate obstetric-gynecological university clinic in Stockholm with patients from the city of Stockholm as well as from the Stockholm county. A pediatrician has been attached to this clinic since 1917. Prematures under 2250 g. are transferred to an infant department in this clinic, accommodating 10 infants, with a special staff taking care of infants only.

*SBBH* is a separate municipal obstetric-gynecological hospital in Stockholm, to which a pediatrician has been attached for some years. Children under 2250 g. are transferred after some hours to one of the four children's hospitals in Stockholm. Practically all the patients come from the city of Stockholm exclusively.

*Södertälje BB* is a lying-in department under the supervision of the head surgeon of a large county hospital in a manufacturing town of 20,000 inhabitants. No pediatrician or obstetrician is attached. Nearly all prematures stay in this department.

*Norrtälje, Väsbyp, and Klingsta* are other fairly large lying-in departments within Stockholm County. They are all under supervision of surgeons. Neither pediatric nor obstetric spe-

cialists are attached. Nearly all prematures stay in the respective hospitals.

In 1944, 1945, and 1946, in these institutions a total of 21851 living children were born, including 1072 prematures.

	ABBH	SBBH	Söderfälje	Other 3
Living children .....	9030	6006	2903	3912
Prematures .....	508	291	142	131

The mortality for the first year of life during this period was 2.52 % in the city of Stockholm, 2.42 % in Stockholm County.

In addition, an account is given of still-birth among children of the same length and weight as those in the above material and within the same period. Further, of the mortality among prematures distributed on the hours of the first day, on the various days of the first week, and on the months of the first year.

The total mortality in the first year of life among children born in the various maternity hospitals was found to be:

ABBH	SBBH	Söderfälje	Other 3
22 %	25.3 %	27.8 %	13.1 %

Leaving out the mortality for the first 6 hours, the result was:

9.1 %	12.8 %	13.5 %	7.3 %
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Trying to illustrate the risk of infection associated with the various forms of care, a comparison was made of the increase in the mortality from the first weeks of life, including the second month. The prematures born in ABBH showed an increase of 1.8 %, those born in SBBH 5.1 %, and in all the county institutions an average increase of 1.5 %.

As pediatric consultant to ABBH as well as SBBH, I had hoped that I would have been able numerically to show that the form of care given in ABBH was the best one for the

prematures. Through a very long time this care has been following acknowledged pediatric laws. The transport from the lying-in department, where the child immediately was placed in an Aga couveuse, to the premature department takes place within some hours and is very short, within the same building. The premature department has a specially trained staff that has no other work to do. Infections occur but very seldom, and the most modern principles of children's care are followed. The patients represent the city of Stockholm as well as the Stockholm county. A comparison between these patients and, on the other side, Stockholmers in SBBH and county children in the aforementioned 4 institutions, however, gave the following result:

Stockholmers	{	SBBH	(284)	25.6 %
		ABBH	(149)	25.5 %
County children	{	ABBH	(323)	19.8 %
		Other 4	(261)	20.7 %

Judging from this comparison, our measures post partum — no matter how essential — are only of very slight importance statistically as compared to all the antenatal factors jeopardizing the prospects of the prematures. These factors of social-economic, epidemic-infectious character, etc. applying to a city population and the inhabitants of a fairly large manufacturing town are obviously of much greater significance than those governing the population of smaller towns and villages. I have also elaborated an account of some of these factors that will be published in some other connection.

#### DISCUSSION

*P. Selander (Sweden).*

With the great interest taken by Scandinavian pediatricians in prematures it is rather remarkable that we have not yet agreed as to what we mean with the term "premature". As a rule, probably this term implies the child who at birth weighs under 2500 g. This, as suggested by Ylppö, is now of 30 years' standing. Often we meet with the statement that this definition is recognized generally throughout the world. But this is not the case.

In 1935 the American Academy of Pediatrics proposed that a premature is a child who at birth weighs  $\leq 2500$  g. The difference is not great, it is true, but there is a difference. We therefore ought to insist that authors of premature-statistical works should state more precisely than now is customary what they mean by premature. I wonder if it would not be suitable for the Scandinavian Pediatric Association exactly to define the concept of prematurity.

Further, we have no uniform classification after weight for the prematures, and this makes it difficult to compare statistical accounts from different countries. Here, too, certain principles would be serviceable, preferably the same weight classes as suggested from U.S.A. by Julius Hess.

*Y. Åkerrén (Sweden).*

The mortality in the premature departments of the Sahlgren Hospital is shown in the following tabulation. These departments are directed by pediatricians attached to the children's hospital in Gothenburg.

The importance of a thorough analysis of all the factors significant to the care of prematures is emphasized especially with regard to the great part played by the early premature mor-

*Premature Children treated in the Premature Departments  
of the Sahlgren Hospital in 1941—48.*

Year	No. of prematures	Died	
1941	201	45	(22.4 %)
1942	216	44	(20.4 %)
1943	190	51	(26.8 %)
1944	274	103	(37.6 %)
1945	304	112	(36.8 %)
1946	283	75	(26.5 %)
1947	251	72	(28.7 %)
1948 $^{1/1} - ^{30}/\%$	163	23	(14.1 %)

tality in the total mortality. We should try energetically to combat the premature mortality so as to obtain a further reduction of the infant mortality.

*C. E. Räihä (Finland).*

I should like to ask whether the frequency of prematures can be seen to differ in the different classes of the population.

From the material of the Helsingfors Maternity Clinic we have

found the frequency of prematures for unmarried mothers to be about 15 %, and the same for married mothers working outside their home, whereas for married mothers who only work at home it is as low as 5 %.

#### A. Ylppö (Finland).

The limit for prematurity was discussed on the last pediatric congress. The upper limit has been established as 2500 g. *inclusive*.

#### I. Alm (Sweden).

In reply to Dr. Räihä I wish to present my classification of the material after social principles.

	Illegitimate in % of all	Mortality	
		Legitimate	Illegitimate
ABBH .....	13.5 %	20.2 %	28.1 %
SBBH .....	19.0 %	24.8 %	29.6 %
County .....	17.6 %	21.8 %	15.2 %

In this tabulation the remarkable feature is the low "illegitimate" percentage for ABBH and the difference between legitimate and illegitimate in the County.

I have also divided the material in social groups: I, unqualified workers; II, qualified workers; III, foremen, etc.; IV-V, "middle class" — "upper class":

	I	II	III	IV-V
ABBH .....	23.3 %	24.6 %	20.7 %	16.8 %
SBBH .....	25.7 %	29 %	21.8 %	18.2 %
Södertälje ....	19.3 %	31 %	41 %	15.3 %
Other hosp. ....	5.9 %	19.7 %	12.5 %	—

There is no established difference, but the tendency is obvious. Some of the groups, however, — the ones that are underlined — are very small, including only 10-20 cases. It is a striking fact that the social group I which is worst off economically, is in the County not the worst with regard to the premature mortality.

## RICKETS IN PREMATURE INFANTS. A CLINICAL AND HISTOLOGICAL STUDY

By

STIG RANSTRÖM, Sundsvall, and GERT v. SYDOW, Uppsala,  
(Sweden).

*Authors' abstract.*

In a previous paper one of the authors (v. Sydow: Acta paediatrica 33: suppl. 2, 1946) showed that in premature infants certain chemical and radiological changes typical for rickets develop during the first months of life. These changes are to a certain extent dependent on feeding, being most marked in infants reared exclusively on human milk. The interpretation given was that the premature infant at birth has insufficient stores of calcium and phosphorus. With human milk it also receives an insufficient supply of phosphorus; and the calcium of the food cannot be absorbed to a sufficient amount if vitamin D is not supplied. In this way a submineralization develops which may result in rickets.

In order to check this interpretation also by histological studies a costochondral junction was removed from each infant autopsied at the obstetrical department of the Sahlgren Hospital in Gothenburg during a period of 2½ years. The material is derived from 182 infants. Of these, 155 were premature and in 99 cases death had occurred during the first two days of life. Most of them had received exclusively human milk.

The histological findings were divided into two main groups, “—” and “+”, sc. those showing normal ossification zones and those showing undeniable signs of rickets. There are, of course, quite diffuse transitions between these groups. It was, however, found that the cases which were designated on

histological grounds as "(+)" or "?" were distributed among the different age groups in the same way as the negative cases, so that for the present they have been considered as belonging to the negative group. The cases in the "+" group naturally showed very varying degrees of severity in the rachitic changes. (This was exemplified by microphotographs.)

It was found that during the first day of life cases designated as "—" form the majority but that they rapidly become less common. Cases showing definite rachitic changes are not uncommon even during the first days, forming one third of the cases during the first 24 hours and half during the second day, but from the third day onwards the great majority shows definite signs of rickets.

The most surprising feature of our results is that no less than 35 percent of the infants dying within two days of birth show definite signs of rickets. According to modern textbooks, congenital rickets is very rare and it is even questioned if it does occur except in the children of mothers with osteomalacia. The mothers of the infants in our series were certainly not suffering from osteomalacia. They probably form a fairly representative cross-section of the population of Gothenburg and their diet during pregnancy seems to have been fairly satisfactory in most respects. All of them stated that they had consumed a lot of milk, usually between  $\frac{1}{2}$  and  $1\frac{1}{2}$  litres a day, but many of them had not taken any vitamin D supply. No doubt, however, many of our infants had their rickets at birth. This fact may be of practical importance in that it places a larger amount of the responsibility for the prevention of rickets on the obstetrician than hitherto.

The frequent early occurrence of histologically demonstrable rickets which has been observed in this study lends support to the assumption that the chemical and radiological changes described in the previous paper are really rachitic in nature and, therefore, also supports the conclusions drawn in this paper, namely, that the insufficient stores of calcium and phosphorus at the time of birth (at least in premature

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infants) combined with insufficient supply of phosphorus in human milk and insufficient absorption of calcium may lead to rachitic changes even in the very earliest days of life.

### DISCUSSION

A. Ylppö (Finland).

The occurrence of congenital rickets has been known and discussed for some time. But it is surprising that this disease is so common as shown by Dr. v. Sydow. The phenomenon of craniotabes which is not infrequent in newborn, is probably to be ascribed primarily to a rachitic process in the bones of the skull, not to mechanical factors as often assumed previously.



## **SECTION IV**

**SUNDAY, AUGUST 15.**

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*From the Pediatric Clinic at Kronprinsessan Lovisa's Children's Hospital, Stockholm.  
Head: Professor A. Lichtenstein.*

## **HEART TOLERANCE TESTS IN CHILDREN\*)**

By

**E. MANNHEIMER and W. GRAF (Sweden).**

*Authors' abstract.*

In our clinic, hypoxia tolerance test, Bing's standard exercise test, and determination of arterial oxygen saturation at rest and after exercise have been chosen in order to estimate the cardiac function in children especially in cases of congenital heart defects with cyanosis.

*Hypoxia tolerance test* is as a rule positive in cases of active carditis of different types. Also the majority of cases of patent ductus arteriosus react with obvious changes in the electrocardiogram. We therefore mean that the test gives information about the functional capacity of the heart in children.

The blue babies react with very few exceptions negatively also in such a low oxygen concentration as seven per cent. This phenomenon has been discussed but no proper explanation is so far available.

*The Bing's standard exercise test* has been used both in normal cases and in different types of cardiac malformations with cyanosis.

The ventilation, oxygen intake, and carbon dioxide produced show somewhat higher values in normal children than in normal adults. The amount oxygen and carbon dioxide per minute and per liter of ventilation is somewhat smaller in children than in adults, the increase during exercise being about the same in both groups. (See table.)

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\* ) The results of these investigations will be presented in 1948 or in the beginning of 1949 as a chapter of the monography *Morbus caeruleus*, edited by E. Mannheimer and published by S. Karger, Basel, Switzerland.

DIAGNOSIS	NUMBER OF CASES	DIFFERENCE $\Delta \text{O}_2/\text{min} / \text{L.V.}$ EXERCISE-REST	DIFFERENCE $\Delta \text{CO}_2/\text{min} / \text{L.V.}$ EXERCISE-REST
NORMAL CASES ADULTS (Gruenwald et al.)	15	+8.0	+0.0
NORMAL CASES CHILDREN 4-10 yrs.	15	+9.2	+8.7
PATENT DUCTUS ARTERIOSUS	15	+9.1	+5.0
TETRALOGY OF FALLOT	12	-4.8	-8.0
EISENMAYER COMPLEX	3	-1.7	-0.9

Results of Bing's Exercise Test in Normal Cases and in Congenital Heart Disease. (All values are average figures for each group.)

In patent ductus arteriosus there is the same type of reaction during exercise as in normal children. (See table.)

In tetralogy of Fallot there is an obvious decrease in the amount of oxygen and carbon dioxide per minute, and per liter of ventilation during exercise, which in full accordance with *Bing et al.* can be explained by the decreased pulmonary flow. (See table.) The resting values in this group are smaller than in normal children which speaks in favour of a decreased pulmonary gas exchange also at rest.

In Eisenmenger complex we have found a small decrease in oxygen and carbon dioxide during exercise. (See table.) This result does not agree with that of *Bing et al.* In our opinion, the result speaks in favour of a pulmonary damage in these cases.

*Arterial puncture and determination of the arterial oxygen saturation* in a van Slyke apparatus at rest and after exercise is of clinical value in cases of morbus caeruleus. Many cases which at rest are only slightly cyanosed and not at all polycythemic show after exercise a marked fall in arterial oxygen saturation. The results obtained in five cases of tetralogy of Fallot showed as an average a fall from 70 to 50 per cent during exercise.

*From the Pediatric Clinic at Norrtull's Hospital, Stockholm.  
Head: Professor A. Wallgren.*

## ON THE TECHNIQUE IN ANGIOCARDIOGRAPHY ON CHILDREN

By

OLIVER AXÉN and JOHN LIND (Sweden).

*Authors' abstract.*

In the Norrtull's Hospital angiography has been performed since 1946, with 70 % diodrast for contrast medium. Prior to each examination two tests are carried out for any possible allergic reaction to this preparation: an ocular test and an intravenous test with  $\frac{1}{2}$ -1 cc. diodrast. Angiocardiography has not been performed on children with any disease of the liver or kidneys or with allergic symptoms in the past or present history. In infants up to six months old, without any cardiac disorder, 6-10 cc. of the remedy was sufficient; for children from 6 months to 2 years old the dosage was 10-15 cc.

The intravenous injection is given into the cubital vein after this is laid bare. In children under 3 months this is generally done under local anesthesia; children over 3 months are usually anesthetized with avertin by rectum. The entire amount of contrast medium should be injected within 2 sec.

Photography with the rays only in one direction gives an overstorage of contrast medium in the various heart chambers, making it more difficult to judge of the pictures. A method for photography with synchronous exposure in two rectangular directions has been worked out in order to obtain a reliable 3-dimensional estimation of the various chambers of the heart. In order to obtain this, in collaboration with the Swedish X-ray firm Georg Schönander, we have constructed a special angiographing table, the principal features of which are as follows: From a horizontal cassette magazine and a vertical one, each containing 10 cassettes, one cassette

from either, are synchronously brought forth under the patient and at the side of him. When the cassettes are in place, they exposed themselves the film to the rays from the roentgen tube above and another roentgen tube at the side. The next pair of cassettes slip forth into the proper position and elicit a new exposure at an interval of 1 sec., and so on. So, with this table 10 pictures are taken in one direction and 10 others are taken synchronously in a rectangular direction to the first ones — all in the course of 10 sec. The patient is examined in lying position, being placed on the table in oblique position so that the X-ray tube above the patient gives a projection corresponding to the left anterior oblique position, and the X-ray at the side of the patient gives then a projection corresponding to the right anterior oblique position. In this way the chambers of the heart and the large vessels are projected to the greatest extent possible.

Demonstration of typical cases.

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From the Pediatric Clinic at Kronprinsessan Lovisa's Children's Hospital, Stockholm.  
Head: Professor A. Lichtenstein.

## ANGIOCARDIOGRAPHY IN FALLOT'S TETRAD

By

F. ULFSPARRE (Sweden).

*Author's abstract.*

In 1888 Fallot described a congenital malformation of the heart with cyanosis that in the literature is designated as Fallot's tetrad. This consists of pulmonic stenosis, interventricular septal defect, overriding of the aorta and hypertrophy of the right ventricle.

In recent years this malformation has proved accessible to operative treatment after Blalock or Pott, emphasizing in this way more strict requirements as to an exact special diagnosis.

In 1937 Castellanos and collaborators gave a method for roentgenological examination of the anatomy and function of the heart by means of contrast medium. Subsequently, comprehensive works on this subject have been published from America. Here I think it will suffice to mention Robb & Steinberg, who employ a more concentrated contrast medium — 70 % diodrast — and Sussman, Grichman & Steinberg, who introduced serial film changes with 6 exposures in rapid succession. These two improvements — a superior contrast medium and more roentgenograms in rapid succession — appear to be some of the conditions for more detailed studies of the heart and for improved diagnostics.

In connection with the adoption of operative treatment for congenital heart defects in this hospital we have carried out angiographic examination of a number of children of 2-16 years. After the directions of the author the X-ray firm Georg Schönander in Stockholm has constructed a simple motor-driven cassette changer with 6 exposures in 6 sec. The

apparatus is placed on an ordinary X-ray table and the under-couch tube is used for the exposures which are released automatically when the cassette is brought into place. Catheterization is performed prior to the angiocardiography and merely by replacing the catheter with a cannule, both examinations may be performed in one seance with employment of the same vein — which means a great advantage. The examination is carried out under universal anesthesia — narcotal — with the patient in lying position.

In our material which comprises chiefly congenital defects belonging to the morbus caeruleus group, angiocardiography appears decidedly to be of value. The present investigation is aimed at the following questions:

1. Simultaneous contrast filling of the aorta and pulmonary arteries establishes the diagnosis of Fallot's tetrad, especially with regard to the differential diagnosis from Eisenmenger's complex — dilatation, not stenosis of the pulmonary artery, interventricular septal defects, overriding of the aorta and hypertrophy of the right ventricle.

2. It establishes whether the aorta is ascending on the right (20 % of the cases) or left side. This is necessary to know before the operation. With sinistroposition of the aorta the operation is performed on the right side, with dextroposition (20 % of the cases), on the left side.

3. In a few cases the overriding of the aorta may be extreme, and then the left ventricle is small and rudimentary. This constitutes a contraindication for the operation as it implies a risk of post-operative pulmonary edema with lethal outcome.

4. Stenosis in the pulmonary conus may often be registered directly, and in many cases there is distinct post-stenotic dilatation of the pulmonary artery.

5. In many cases the appearance, course, and length of the systemic arteries may be given in this way, affording thus a guidance for the operative measure.

These points are illustrated by demonstration of a number of radiograms.

Angiocardiography was performed in 34 cases, and only in one of these was there a transitory urticarial exanthema.

In our opinion the angiocardiographic examination is of unquestionable value in ascertaining the congenital defects of the heart belonging to the *morbus caeruleus* group, establishing the diagnosis and giving the degree of overriding of the aorta and thus, in some cases, contraindicating surgical treatment. The position of the stenosis may be established, and the radiogram gives an idea as to whether the pulmonary artery and the systemic artery are suitable for operative measures.

*From the Pediatric Clinic at Norrtull's Sjukhus, Stockholm.  
Head: Professor A. Wallgren.*

## DETERMINATION OF THE HEART VOLUME ON INFANTS

By  
JOHN LIND (Sweden).  
*Author's abstract.*

The material comprises 267 normal children under 1 year. The children were examined lying on their back, with arms and legs fixed, the arms being extended over the head with simultaneous exposure in frontal and side views, released by the examiner at the side of the patient at the suitable moment.

The measurement and calculation of the heart volume were carried out with employment of the Rohrer-Kahstorf method as modified by Jonsell (planimetric measuring of the frontal heart shadow is replaced by its calculation after the formula for an ellipse). The error of the method, calculated in the usual way from 35 duplicate determinations, without regard to the cardiac and respiratory phases amounts to  $\pm 5\%$ .

In order to study the variations in the heart volume under the heart cycle, serial photography with synchronous photography in the rectangular plane was carried out. At the same time an electrocardiogram was taken with marking of the exposure by means of a photo-cell covered by a fluorescent screen and placed in the ray field. The maximal deviation from the average volume calculated for the series, in the 7 cases examined, amounts to 7,6 %, and on the calculation of the mean value for the maximal deviation in each series it amounts to 5,7 %.

In order to see whether the normal breathing and the change in the position of the heart associated herewith may have any influence on the heart volume, 10 duplicate determinations were performed in inspiration and expiration. By means of electrocardiographic control, those cases were ex-

**Heart Volume Per Square Meter  
of Body Surface and Per Kg.  
Body Weight at Different Ages**

n	Age (days)	Heart Volume			
		ml/ m <sup>2</sup>	ml/ m <sup>2</sup>	ml/ kg	ml/ kg
26	Prematures (<2500g)	200±4,3	180-225	14±0,39	12,0-16,0
138	0-90	230±2,3	205-260	14±0,16	12,0-16,0
39	91-180	260±4,9	230-295	14±0,26	12,0-15,5
64	181-365	260±4,9	225-300	12,5±0,23	10,5-14,5

cluded in which it would be reasonable to expect a considerable difference in volume owing to the different heart phases. The average difference for the 10 cases, expressed in per cent of the inspiratory volume, was 5,2 % and this difference has not been systematic insofar as sometimes the inspiratory volume was the larger one, sometimes the exspiratory. On the whole, variations of the depth measurement compensate the postural changes in the frontal outline of the heart shadow.

In order to obtain an approximate idea about the accuracy of the method, some control examinations were performed on cadavers. In 10 cases fluid paraffin was injected into the heart after the death of the patients. In order to get the posterior border of the heart a thin tube was introduced into the esophagus. The roentgenologically determined volume was compared with the displacement of the heart removed from the body. The maximal deviation amounted to 12 %, the average to  $\pm 4 \%$ .

The material is presented in the tabulation, which gives the number of children examined. The heart volume is expressed in ml. per m<sup>2</sup> body surface and in ml. per kg. body weight; and the mean error for the respective values

is added. Further, the limits for the mean value  $\pm$  are given. The heart volume per  $m^2$  body surface increases slowly, whereas the heart volume per kg. body weight keeps constant, showing a slight decrease in the last quarter. Perhaps this may be explained as follows: when the child increases proportionally in size, also the mass increases and, with this, the weight per surface unit.

#### **Summary.**

Determination of the heart volume on infants is a simple measure that takes but little time and is serviceable for practical, clinical use. The accuracy of the method is sufficient for this purpose, even though the determination is made without regard to the cardiac and respiratory phases.

### **DISCUSSION**

#### *E. Mannheimer (Sweden).*

With reference to the most interesting paper by Drs. Axén & Lind I wish to thank for the cardiologic cooperation which has existed for some length of time between the Norrtull Hospital and the Crown-Princess Lovisa's Children's Hospital.

We have performed angiography in connection with catheterization and I wish to emphasize the significance of the following points:

- 1) that the angiography has been performed under anesthesia;
- 2) that the problem involved is clearly defined before examination;
- 3) that in the cyanotic congenital heart defects, in all not quite typical cases, angiography and catheterization should be carried out before it is decided to treat the patient surgically.

#### *C. E. Räihä (Finland).*

The heart volume increases with increasing age, calculated per  $m^2$  body surface, and it is less in prematures than in children born at term. The same applies to the basal metabolism. As both these observations correspond, they lend support to each other.

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From The Children's Hospital, Martinsvej, Copenhagen.  
Head: A. Rothe-Meyer, M. D.

## INVESTIGATIONS ON POTASSIUM IN INFANTS\*)

By  
**AGNER SVENDSEN** (Denmark).

*Author's abstract.*

The potassium has been estimated in ashed heparine plasma after the method of Van Slyke and Rieben with precipitation by phosphor-12-tungstic acid. The blood has been taken 3 hours after a meal.

In five fullborn (birth weight 28-3500 g.) and nine pre-matures (birth weight 19-2300 g.) at Children's Hospital, Martinsvej, Copenhagen, the potassium content of plasma was estimated at intervals of eight days (in some cases 14 days). The following mean values have been found:

	1' week of life	2'-8' week of life
Prematures .....	16,3 mg%	18,0 mg%
Fullborn .....	18,9 mg%	17,9 mg%

Oral administration of 15 cg. KCl pr. kg. body weight causes, just as in adults, an increase of T<sub>1-2</sub> in the ECG. Infants show a smaller increase than adults and do not react to a dosage of 10 cg. KCl pr. kg. The T-wave has been found normal again three hours after ingestion. The increased T after KCl ingestion is caused by a higher concentration of potassium in the myocardium.

After administration of glucose and insulin the deposition of glycogen in the liver requires a large amount of potassium; causing a loss of potassium in other organs. In experiments in adults I have found such a decrease of the potassium in the plasma followed by a decrease of the T<sub>1-2</sub>. The author

\*) Is to be published elsewhere.

therefore considers the decrease of  $T_{1-2}$  as a sign of a decreased potassium concentration in the myocardium.

In nine infants aged 1-3 months, suffering from toxicosis, the ECG and potassium of the plasma have been examined at intervals of 2-4 days. In three cases examined on the first day of illness, the potassium was increased in the plasma. The T-wave at this time already was decreased in two of these cases, the third one only showing the decrease of  $T_{1-2}$  on the following examination two days later. During the course of the disease there always appears a decrease of the potassium in the plasma.

Six cases, in which the first examination was made 3-8 days after the beginning of the symptoms, showed  $T_{1-2}$  below 0,1 mm and low or decreasing potassium levels in the plasma (min. 7,4 mg%). During the recovery an increase is found in the potassium concentration of the plasma and in  $T_{1-2}$  wave.

The increased potassium content in plasma on the first day of illness is due to an increased permeability causing a decrease of the intracellular concentration and an increase of the extracellular concentration of potassium. The low  $T_{1-2}$  is a sign of a reduced content of potassium in the myocardium. The lowering of the plasma potassium during the course of the toxicosis is a sign of an increased potassium excretion.

The author suggests that the variations of the T-wave correspond exactly to the variations of the potassium in the myocardium.

*From the Children's Hospital, Fuglebakken, Copenhagen.*

*Head: Vald. Poulsen, M. D.*

*and the Pediatric Clinic at Norrtull's Sjukhus, Stockholm.*

*Head: Professor A. Wallgren.*

## THROMBOOPENIA IN CHILDHOOD

By

SVEND HEINILD (Denmark) and MAJ LEVANDER LINDGREN  
(Sweden).

*Authors' abstract.*

A catamnestic investigation is made of all the cases of thrombopenic purpura registered during a period of 25 years in pediatric clinics in Copenhagen, Gothenburg, Stockholm and Uppsala. The material comprises 113 patients, and is the largest one published so far. The observation period varies between 1 and 28 years, averaging 9.4 years.

Revision of the anamnesis, course, and follow-up examinations gives the following classification of the material:

	Died
Infectious (or postinfectious) thrombopenia . . . . .	63      13
Systemic diseases . . . . .	9      7
Acute, essential thrombopenia . . . . .	28      1
Chronic, essential thrombopenia . . . . .	13      0
Total . . . . .	113      21

### I. *Infectious (Postinfectious) Thrombopenia.*

This group includes all the cases in which an infection could be demonstrated immediately before the first appearance of the thrombopenic hemorrhagic condition (as a rule, 1-2 weeks before).

Age at first appearance	No. of patients	Died
Years		
0- 2 .....	20	10
3- 5 .....	23	1
6- 8 .....	7	1
9-11 .....	10	1
12-14 .....	3	0
	63	13

The character of the infections is evident from the following list:

Infections of the upper respiratory passages (often streptococcus infections) .....	21
Tuberculosis .....	9
Sepsis .....	7
Calmette vaccination .....	3
Rubeola .....	2
Parotitis .....	2
Wound infection .....	2
Diphtheria .....	1
Measles .....	1
Varicellae .....	1
Infections of unknown character .....	14

The mortality is alarmingly high in infancy, in which the infection most often has the character of sepsis. On reexamination the surviving infants were clinically well, but 6 of the 50 showed subnormal platelet counts (< 150,000) though with normal bleeding time.

## II. Systemic Diseases with Thrombopenia.

This group includes only cases which in the hospital were recorded as thrombopenic hemorrhagic purpura, *i.e.*, not cases of thrombopenia appearing during the course of well-

diagnosed systemic diseases, leukoses, etc. The diagnoses were as follows:

	Patients	Died
Aplastic anemia .....	3	3
Leukemia .....	2	2
Megaloblastic anemia .....	1	1
Malignant tumor ? (no autopsy) .	1	1
Hepato-splenomegaly .....	1	0
Splenomegaly .....	1	0

### III. Essential Thrombopenia, Acute and Chronic.

This group includes all cases in which no etiological factor could be demonstrated, while the clinical picture does not differ from the one encountered in the well-known reaction of medicamental hypersensitivity to quinine, sedormid, gold, sulfathiazole, etc. and in the benign infectious form. The acute form is cured definitively after 1-6 months. The chronic form takes an intermittent course with symptom-free periods of up to 7 years. Recurrence seems often to appear in connection with an infection. The age distribution of the cases was as follows:

Age at first appearance	No. of patients	Died
0- 2 years .....	10	1
3- 5 > .....	15	0
6- 8 > .....	4	0
9-11 > .....	6	0
12-14 > .....	6	0

On reexamination all the acute cases showed normal platelet counts, whereas some of the chronic cases showed subnormal values (< 150.000), and in 2 the bleeding time was prolonged — but all of them were free from symptoms.

Splenectomy was performed in 12 cases, with the following results:

Diagnosis	No.	Recovery	Relapse	Died
Infectious thrombopenia .....	3	1	1	1
Essential, acute thrombopenia ..	1	1	0	0
— chronic thrombopenia ...	4	3	1	0
Splenomegaly .....	2	1	1	0
Leukemia .....	2	0	0	2

### Conclusion.

Thrombopenic purpura in childhood is a benign disease — apart from the acute infectious septic forms in infancy. We here have the impression that it is more the infection *per se* than the hemorrhagic diathesis that is decisive of the outcome. The prognosis depends on the primary lesion, and the thrombopenia is to be looked upon as a symptom. In the so-called essential forms, thorough pathogenetic studies are still wanting. In the present work the clinical resemblance is pointed out between the positively verified infectious form of the disease and the positively verified reaction of medicamental hypersensitivity. We are somewhat reserved as to the value of splenectomy, which conceivably may have a true curative effect in the relatively few cases of a solitary or dominating tumor of the spleen (splenomegalic medullary inhibition). Still, it seems as if the indication for splenectomy has to be made a little broader, applying also to girls with menorrhagia in puberty.

Owing to the here demonstrated benign character of thrombopenia outside infancy, the previous therapeutic statistics, splenectomy inclusive, that failed to take a corresponding classification into consideration, are not of much value and often misleading.

### DISCUSSION

*Y. Åkerrén (Sweden).*

In the Gothenburg Children's Hospital, in the last half year we have observed a number of cases of thrombopenia in newborn. In all the cases where the thrombopenia was uncomplicated, im-

provement appeared spontaneously. In these cases the hemorrhagic diathesis has been slight. The most conspicuous manifestations were a large intracranial hematoma in one case, slight melena in one case. Reports in the literature about congenital thrombopenia being rare are erroneous and probably due to the circumstance that a platelet count is performed on the newborn but seldom.

*L. Salomonsen (Norway).*

emphasizes the relatively great frequency of the postinfectious thrombopenia in comparison to essential thrombopenia.

In estimating the degree of thrombopenia in the newborn it should be taken into consideration that the number of thrombocytes is lower in the newborn than in older children.

*From the Department of Obstetric and Gynecology at Sahlgrenska  
Sjukhuset, Gothenburg.  
Heads: Professor E. Jerlov and H. Frederikson, M. D.*

**ON THE OCCURRENCE OF MASSIVE ASPIRATION IN THE  
LUNGS OR OBTURATING CONTENTS IN THE TRACHEA  
AND MAIN BRONCHI IN INTRAUTERINE AND NEONATAL  
ASPHYXIA**

By  
**G. LUNDH (Sweden).**  
*Author's abstract.*

Systematic autopsy in all perinatal deaths in the maternity hospitals in Gothenburg has been performed since September 1. 1947, among other things with regard to the changes mentioned under the heading. Among 98 examined cases, of which 58 children had died before or during the parturition and 40 had been delivered alive but died immediately after birth, the following observations were made which could be tabulated summarily:

1.	<i>Massive aspiration</i> (to the lung parenchyma)	cases
	a) <i>without obturation of air passages</i> .....	33
	b) <i>with obturation of air passages</i> .....	13
2.	<i>Slight or no aspiration</i> (to the lung parenchyma)	
	a) <i>without obturation of air passages</i> .....	46
	b) <i>with obturation of air passages</i> .....	6
	<b>Total .....</b>	<b>98</b>

From this tabulation, among other things, the following points are evident:

1. Massive aspiration appears to be more common than obturating contents in the air passages, occurring in 46 out of 98 cases, while obturating contents in the air passages was seen only in 19 cases.

2. The frequency of obturating contents is higher among the cases with massive aspiration than in cases with slight or no aspiration.

3. In the group with slight or no aspiration to the lung parenchyma itself, obturating contents in the trachea or main bronchi were found only in 6 out of 52 cases.

4. These observations appear to be of interest, among other things, considering the question of employing intratracheal measures with a catheter or some other instrument in the treatment of asphyxia in the newborn. Insofar as these measures aim to remove the obturating contents from trachea and main bronchi they seem to have been indicated, but very seldom. In cases with massive aspiration to the lungparenchyma the removal of obturating contents from the trachea and bronchi is probably of little value. In the absence of massive aspiration to the lung parenchyma, the occurrence of obturating contents in the trachea and main bronchi is relatively rare.

(A more detailed report on this subject by Y. Akerrén and G. Lundh will be published elsewhere.)

*From the Department of Obstetric and Gynecology at Sahlgrenska  
Sjukhuset.*

*Heads: Professor E. Jerlov and H. Frederikson, M. D.,  
and from Barnsjukhuset, Gothenburg.*

*Head: Y. Åkerrén, M. D.*

### ASPHYXIA NEONATORUM\*)

*Resuscitation by the Supply of Oxygen to the Ventriculus.*

By

NILS FÜRSTENBERG (Sweden).

*Author's abstract.*

The commonest causes of failure of an infant to breathe at birth are:

- (a) anoxia, due to inter-uterine asphyxia,
- (b) toxic effects of drugs (administered before or during delivery),
- (c) cerebral hemorrhage,
- (d) prematurity.

Common to all of these is a functional disturbance of the respiratory centre. Irrespective of the primary cause of the asphyctic condition, the apnea — the predominant symptom in neonatal asphyxia — aggravates the anoxemia and thereby starts a vicious circle.

The only way to arrest this reciprocal continuation is to increase the oxygen content of the blood, but partial or complete respiratory failure as well as atelectasis renders an extraneous supply of oxygen difficult.

In severe cases of asphyxia respiration cannot be induced by ordinary measures such as rubbing and gentle slaps, thermal stimuli or drugs. For that reason American obstetricians recommend the aspiration of the mucus and fluid by means of a tracheal catheter, and subsequent gentle insufflation of the trachea with oxygen. The fear of possible injury due to

\*) A more detailed report will be published elsewhere.

lack of adeptitude seems to account for the relatively limited application of this technique in other countries.

In Sweden, where the intratracheal technique is not used, we have tried a method suggested by Åkerrén, according to which oxygen is supplied direct to the ventriculus. Ylppö, Helsingfors, recommended this method for apnea in premature infants. The surface of the mucous membrane of the stomach is comparatively large and well vascularized, and both theory and experiments speak for the assumption that oxygen supplied to the stomach may diffuse into the blood.

Åkerrén elaborated Ylppö's method and suggested the use of two catheters, one for the intake of oxygen and one for the escape of excess oxygen that would otherwise cause undue distension of the stomach. This method has been applied at the Obstetric Depts., Sahlgren Hospital, for the last year during which several cases of severe asphyxia — even with 5-15 mins. total apnea — have been treated successfully. In some cases the newborn was even growing cyanotic before the commencement of respiration.

The method is simple and can be applied without harm to the baby. Results hitherto obtained seem to be encouraging.

#### DISCUSSION

##### A. Ylppö (Finland).

Among the reasons for asphyxia, here we have to mention also the so-called "vernix membrane" and extensive parenchymatous hemorrhages in the lung. In these conditions the absorption of oxygen through the pulmonary mucous membrane is impossible.

##### V. Åkerrén (Sweden).

With reference to Professor Ylppö's emphasis of the importance of the vernix membrane as obstruction to the breathing in asphyxia, it is to be pointed out that these occur only in small prematures who have lived and *breathed*. In asphyxia immediately post partum this condition plays no particular rôle.

The significance of close collaboration between obstetricians and pediatricians in questions of asphyxia is to be emphasized.

With regard to the sensitiveness of the "higher" cerebral centers to hypoxia, undoubtedly it is important to try as quickly as pos-

sible to abolish the deleterious hypoxia. This is important not only with regard to the immediate prognosis but also to the normal psychomotor and mental development of the child.

*A. Wallgren (Sweden).*

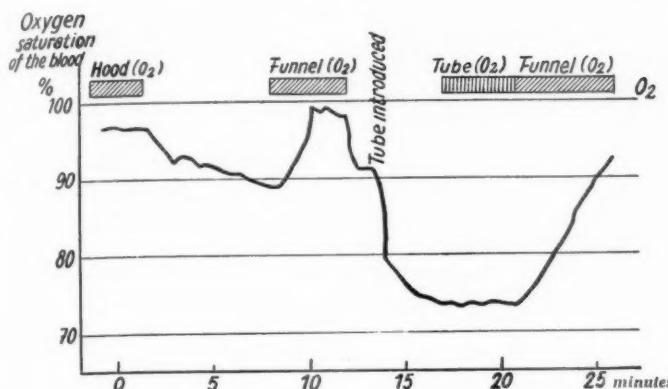
It is an extraordinarily important subject Dr. Fürstenberg has taken up and I think we should be thankful to him for ventilating this question at a pediatric congress. It is, I think, even worth considering as a possible main subject to be discussed at our next congress. The studies reported by Dr. Fürstenberg are very interesting, and if the method proves to keep what it promises, it is of great practical importance. There are a couple of questions, however, about which I should like to hear what the experts think. Is oxygen known for sure to be absorbed through the mucous membrane of the stomach in the newborn in such an amount that it may play any rôle? Of course, this mucous membrane is not directly comparable to the mucous membrane of the air bladder in the fish species mentioned by Professor Ylppö. The latter is formed for absorption of oxygen, the former hardly. Furthermore, I should like to ask if not the irritation which the insufflation of oxygen into the stomach presumably gives rise to may play a rôle in the establishment of the respiration? It would be of interest to try out the same methods but with employment of air instead of oxygen.

*P. Karlberg (Sweden).*

In recent years it has been possible by means of oxymetry easier to study the effect of various forms of oxygen therapy, by means of the oxymeter, which is a double photo-cell colorimeter. It is possible without blood samples to be able to read the variations directly in the saturation of the blood with oxygen.

In the Norrtull Sjukhus in Stockholm we have followed the effect of different forms of administration of oxygen by oxymetry in 5 cyanotic infants,  $\frac{1}{2}$ -14 days old. In all the cases the supply of oxygen by means of a double tube introduced in the stomach (fasting) made the oxygen content of the blood increase only by 0-1 %, slowly and questionably, whereas administration of oxygen by means of a one-liter plastic hood or ordinary glass funnel has given an increase amounting to 5-10 %. (One of the experiments is recorded in the Fig.).

Unfortunately the oxymeter requires warming of the ear for 5-10 min. before the reading, and hence it cannot be employed in cases calling for immediate treatment. Still, these studies appear to indicate that if the child has commenced breathing even in the slightest way the increase in the oxygen content of the inspiratory



air has a considerably greater chance of increasing the oxygen content of the blood than they by administration of oxygen through a tube to the stomach. Therefore the tube treatment should always be combined with oxygen supply through funnel or hood.

*Y. Åkerrén (Sweden).*

Mentioned some experimental and clinical observations which suggested that an exchange of gases and, among other things, absorption of oxygen may take place in the stomach and intestine. On ingestion of oxygen we may reckon that the oxygen also enters the intestine, increasing thus the mucosal surface through which the gas exchange may take place.

*Y. Åkerrén (Sweden).*

The method of administration of oxygen to the stomach might appear to become successful only in cases where physiologically complete atelectasis persist. When this condition begins to yield, the air passages will be the adequate and proper way of oxygen supply.

*C. E. Räihä (Finland).*

I think that the newborn organism may be able to live without oxygen supply longer than the older organism; the metabolism keeps on in a fetal stage. I have seen one case of oesophagotracheal fistula in which the lungs were filled with water on probing and then failed to breathe for about 30 min. Still, after the treatment with artificial respiration was given up as hopeless, the child commenced breathing. Even the heart action was undemonstrable by auscultation or palpation for several minutes.

*From the Pediatric Clinic at Norrtull's Sjukhus, Stockholm.  
Head: Professor A. Wallgren.*

## A STUDY OF RENAL FUNCTION WITH THE AID OF RADIOACTIVE PHOSPHORUS

By  
**L. STRÖM** (Sweden).  
*Author's abstract.*

The biological transformations of carbohydrate proceed at least in part through a series of phosphorylated intermediates. The nature of this chain of intermediates has been more completely elucidated in recent years as new members were discovered. Disturbances of the related phosphorylation processes lead to grave alterations in the metabolism of the organism. Such a disturbance is found, for instance, in diabetes; according to Lundsgaard, insulin plays an important part in the phosphorylation of carbohydrates. Moreover, there is an alteration of the normal phosphaturia which, upon further investigation, appears to be dependent on the condition of the excretory organs, the intestines and the kidneys.

The function of the kidneys in the regulation of the acid-base balance takes place not only through the secretion of sulfate, sodium and ammonia, but also through phosphate secretion, thereby transforming alkaline phosphate to acid.

Serum inorganic phosphate, which in children amounts to 5.0-6.5 mg. per cent, varies with the utilization of carbohydrate. This is the result of the binding of carbohydrate with phosphoric acid to form hexose phosphates, which play an important rôle in the intermediate carbohydrate metabolism. Increases of serum phosphate occur with inflammation of the kidneys and are symptoms of renal insufficiency. The cause of this phosphate retention cannot be definitely stated. It is not simply a result of a disturbance of the secretion and excretion capacity of the kidneys. The diminished excretion of

phosphoric acid by the kidneys with the corresponding increase in the blood and tissues is an important factor in the development of acidosis in cases of renal insufficiency. Thus it is understandable that a poor kidney function can signify a dangerous complication in diabetic acidosis.

Greater knowledge of the use of isotopes has provided in recent years a valuable tool in physiological and biochemical studies. Of the radioactive isotopes, radioactive phosphorus  $P_{32}$  has found wide application, for its half life of 14 days is just long enough to permit the history of the phosphorus atom to be easily followed in the organism.

Hahn, Hevesy, and Lundsgaard (1937) demonstrated in studies with rabbits that parenterally administered radioactive phosphorus is partly stored in the organism and partly excreted. After approximately four weeks, 45 per cent is excreted in the urine and 11.5 per cent in the feces. Möllerström studied the earliest time that radioactive phosphorus begins to appear in the urine after oral administration of  $P_{32}$ . With prior administration of glucose, phosphate appeared in the blood within 10 minutes, predominantly in organic form. In the urine, the excretion likewise began after 10 minutes; and at the end of the first hour, the isotope excretion had risen to considerable levels. In the investigations on diabetics at the Wenner-Grens Institute in Stockholm, it was observed that the excretion curves of a number of patients deviated noticeably from the majority of cases. These patients were found to have renal damage, as was to be expected. These studies therefore suggested that radioactive phosphorus may, through measurement of phosphate excretion, be clinically applicable as a kidney function test.

The following phosphate excretion studies were conducted on about 50 children at Norrtull Hospital after intravenous injection of  $P_{32}$  (sodium phosphate in glucose). The experiments were carried out as follows: into the fasting stomach was introduced 300-500 cc. of water, depending on the age of the child. After 30 min., the urinary bladder was emptied and the radioactive phosphorus was injected. Blood specimens were taken after 1 minute,  $\frac{1}{2}$ , 1, 2 and 3 hours. If a suitable

amount of radioactive phosphorus (approximately  $\frac{1}{20}$  milliecurie) is employed, it is convenient to use a capillary blood sample of 0.2 cc. The urine samples were taken at 5, 10, and 15 minutes after the injection, and thereafter simultaneously with the blood tests. The radioactivity of the specimens was measured in the usual way in a Geiger-Müller counting-chamber and the specific activity, i. e., the relation between impulses per unit volume and the corresponding amount of phosphorus in milligrams in the same unit volume, was calculated. It was shown that the specific activity in urine was significantly greater than in blood. Möllerström explained the latter as that the radioactive phosphate in the urine arises from another more active substance which exists in blood in small amounts but which is continually split in the kidney. Normally, the greater portion of this activity disappears in the first two hours, while the excretion in the urine becomes much greater in the corresponding period.

Specific activity in blood and urine after intravenous inj. of  $P_{32}$ , (0.05 mC).

*Table 1. B. C. 12 years of age. Normal case.*

Time	Blood			Time			Urine			
				Orthophosphate			Total phosphate			
	P	I	I/P	P	I	I/P	P	I	I/P	
8,50	170	599	3,5	8,55	78,6	264	2,1	78,6	202	2,6
9,20	184	284	1,5	9,00	1360	9620	7,1	1019	8010	7,9
10,20	170	207	1,2	9,05	607	2478,7	4,1	361	1480,8	4,8
11,20	184	141	0,8	10,20	148,6	408	2,7	155,9	675	4,3
12,20	176	106	0,6	11,20	85	224	2,6	29,1	272	3
				12,20	841	731	0,9	978	1150	1,2

P = gamma phosphorus/cc. I = radioactive impulse/cc.

I/P = specific activity.

In the cases where acute nephritis had resulted, it first appeared as if the excretion of the organically-bound — as well as the orthophosphate — had greatly diminished.

Simultaneously with the improvement of the clinical symptoms, the excretion of the phosphate had increased.

The following is a typical case of nephritis. See Table 2.

*Case:* S. H., 14 years old. Diagnosis: Nephritis acuta. Became ill at end of September. Admitted to hospital October 2, 1946.

*Urine:* Albumin positive. *Sediment:* 50 red blood corpuscles G. f. *Rest nitrogen:* 56 mg. per cent. Very flat excretion curve. A new test was made on 16/11. Albumin still positive.

*Sediment:* 20-30 red blood corpuscles. *Rest nitrogen:* 46 mg. per cent. The excretion curve is now apparently normal.

Table 2. S. H. 14 years of age. Nephritis acuta.

October 6 Time	Blood			Time	Urine					
					Orthophosphate			Total phosphate		
	P	I	I/P		P	I	I/P	P	I	
8,10	224	694	3,1	8,15	438	87,2	0,19	445	89 0,2	
8,40	432	1166	2,7	8,20	437	251,9	0,59	489	342,3 0,7	
9,40	236	519	2,2	8,25	196	52,9	0,27	128	38,4 0,3	
10,40	178	320	1,8	9,40	302	45,4	0,15	318	63,6 0,2	
11,40	169	203	1,2	10,40	116	17,5	0,16	76	22,8 0,3	
					11,40	186	18,6	421	42,1 0,1	

November 16.

9,00	172	619,2	3,6	9,05	84	176,4	2,1	86	194,4	2,3
9,30	322	579,6	1,8	9,10	864	4579,2	5,3	989	5630,4	5,7
10,30	140	168	1,2	9,15	609	2862,3	4,7	536	2626,4	4,9
11,30	132	108,8	0,9	10,30	142,6	413,5	2,9	243,4	1069	4,4
12,30	180	108	0,6	11,30	113	313,6	2,8	110	330	3
					12,30	362	259,6	0,8	263	289,4 1,1

It is of interest to discover whether the excretion of phosphorus and rest nitrogen is correlated with the edema. Further investigations may perhaps elucidate these questions.

*From The Children's Hospital, Martinsvej, Copenhagen.  
Head: A. Rothe-Meyer, M. D.*

**ESTIMATION OF KIDNEY FUNCTION IN INFANCY BY  
MEANS OF PARA-AMINO-HIPPURATE CLEARANCE AND  
INULIN CLEARANCE\*)**

By  
**JØRGEN VESTERDAL** (Denmark).  
*Author's abstract.*

**Technique.** PAH\*\*) and inulin have been injected subcutaneously and estimated in urine and capillary blood. 0.2 ml heparin plasma is sufficient for double assay of both PAH and inulin. After removal of the proteins by a Zomogy precipitation, inulin is estimated by Kruhøffer's modification of Seliwanoff's reaction, and PAH by Bratton & Marshall's method (modified by C. C. Jensen).

Dose within the first 3 weeks: 0.25 g. PAH and 10 ml. 10 % inulin (Astra). 3 weeks-2 months: double dose.

13 experiments with 2-4 catheterizations have been carried out, and in 3 experiments permanent catheterization has been employed, and by this technique 6-8 clearance periods have been obtained.

**Results.** In infants aged 3 days, PAH clearance was about 50 ml./1.73 m<sup>2</sup> and inulin clearance about 14 ml./1.73 m<sup>2</sup>. Both values increased 2-4 times during the first 2 months. Filtration fraction was rather high (0.25-0.35). No significant difference between prematures and full term infants was observed.

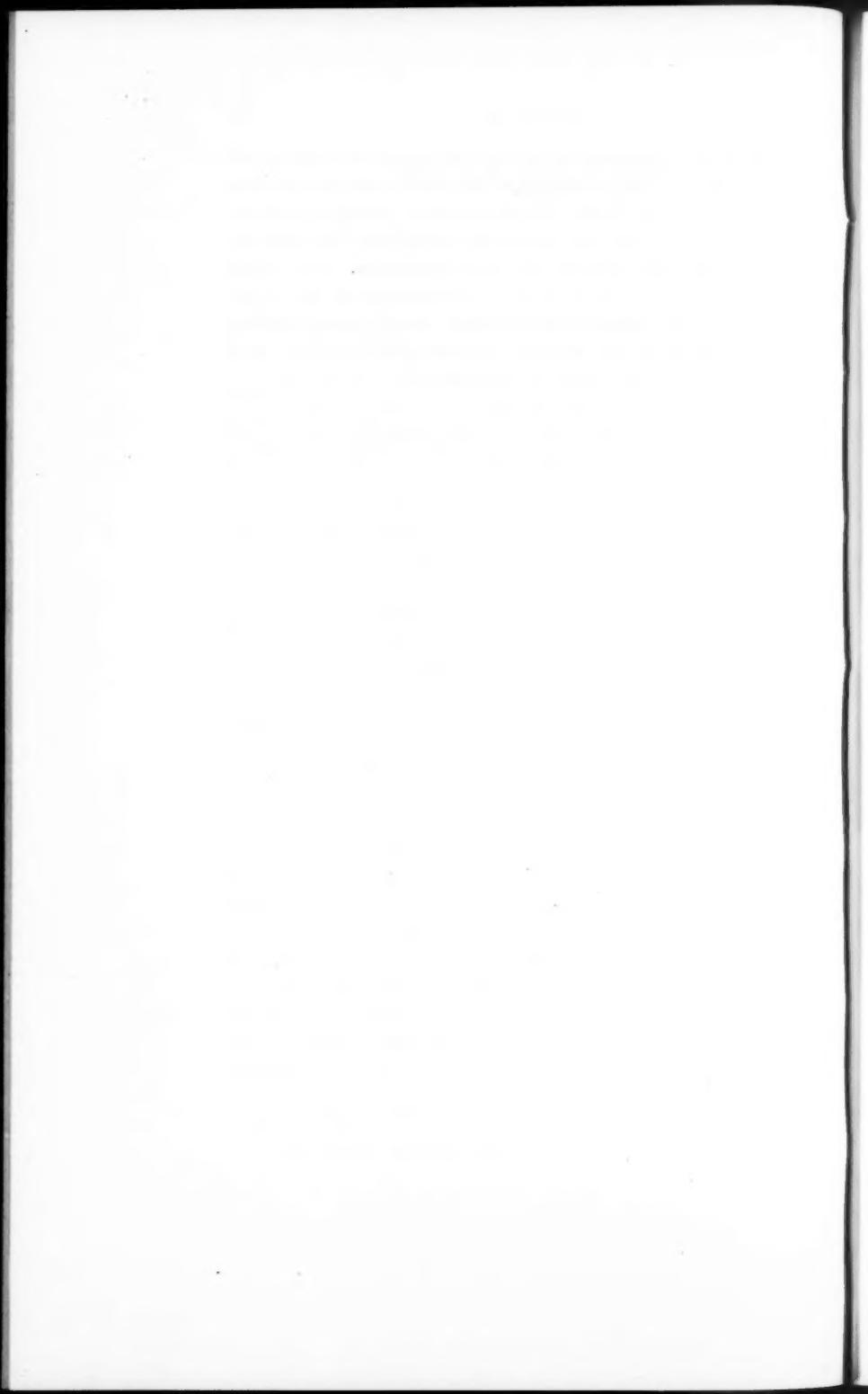
In the experiments with permanent catheterization, 50 ml. 5 % glucose solution was injected subcutaneously, and after that a distinct increase of both PAH and inulin clearance without alteration of filtration fraction was seen in 2 cases.

\*) Preliminary report. Further investigations are to be published in *Acta Pædiatrica*.

\*\*) most kindly supplied by Løvens kemiske Fabrik.

probably due to alteration of the blood supply to some of the nephrons. (It cannot be excluded from these experiments that this was due to contraction of some kidney vessels at the beginning of the experiments, caused by pains from the subcutaneous injection, but *Tudvad* has in experiments with inulin clearance confirmed that there is a real increase of this clearance with higher diuresis.) In the third infant treated in this way, no increase of the clearances was observed; this child had a very highly developed kidney function for its age.

It is suggested that in the newborn the blood vessels of all the nephrons are not open at the same time, but later, when the kidney function is well developed, all of them are patent.



## **SECTION V**

**MONDAY, AUGUST 16.**

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*From the Children's Clinic, Helsinki.  
Head: Professor A. Ylppö.*

## TREATMENT OF ANAEMIA WITH PLASMA FROM DEOXYGENATED BLOOD

By  
ARVO YLPPÖ (Finland).  
*Author's abstract.*

At the beginning of the century *Carnot* and *Deflandre* discovered, that plasma from anaemic animals contained substances, which after injections in experimental animals produced an increase of erythrocytes.

This phenomenon probably depended on shortage of oxygen in the tissues. These same substances, which we here call "*haematopoetins*" could also be found in animals, which had been subjected to artificially low atmospheric pressure and had so become polycytaemic.

At the "Children's Clinic" and the "Physiological Institute" in Helsinki these haematopoetins have been especially studied recently.

They have been found in increased amounts in foetal plasma (Karvonen), in the plasma of patients with decompensated heart failure (Jalavisto and Roschier), and in the plasma of polycytaemic children with congenital heart diseases (Bonsdorff).

Further Bonsdorff has shown, that in normal blood, which has been deprived of its oxygen in a vacuum-apparatus these haematopoetins are produced and they are capable of increasing erythrocytes in experimental animals.

After these positive experiments with animals we have tried at the Children's Clinic to use this so-called vacuum-blood and especially vacuum-plasma in the treatment of anaemia in children.

In practice we have used *human citrated blood*, which was

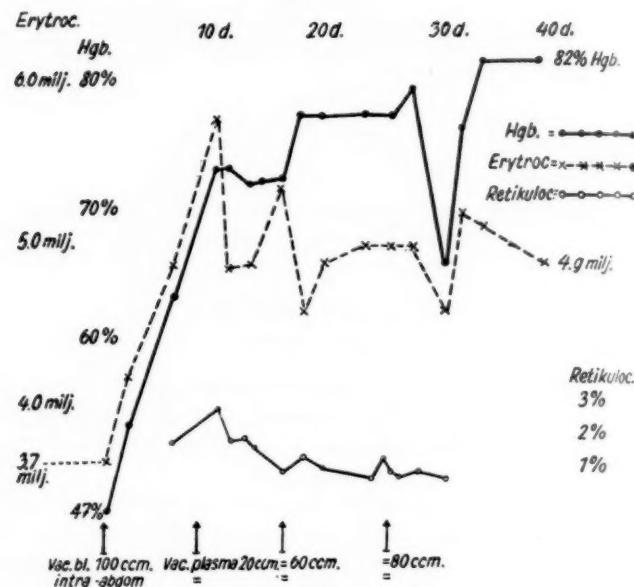


Fig. 1.

kept for about two hours *in a vacuum-apparatus* and thus deoxygenated. The pressure in the apparatus towards the end of the evacuation was only 1-3 mm Hg. So the blood was practically quite free from oxygen. The blood was then centrifuged and as soon as possible injected into children either intra-abdominally or intravenously. The quantity varied from 50-100 ccm injected at intervals of from 5-8 days.

We gave these injections to 12 children. They were all severe cases, mostly infants, prematures, badly developed, or chronically anaemic children with a haemoglobin content varying from 11-50 % Sahli.

From most of these cases we could not get any clear results. Although in some cases an increase of haemoglobin was noticeable at first diarrhoea and other nosocomial infections disturbed our final results.

In two children with severe aplastic anaemia we could see

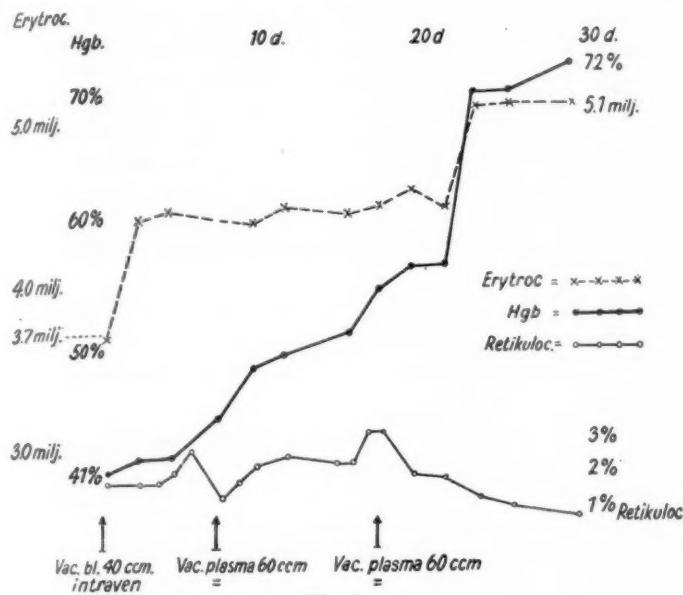


Fig. 2.

after vacuum-blood-injections haemoglobin increase from 15-45 %, but the final result in these unfavorable cases was negative.

Positive results were seen in three cases. Details are given in Figs. 1-3.

They were all chronic-anaemic premature children, as the following short descriptions show.

**Case 1 (Fig. 1.)** Jarmo P. 14 months. Weight 11.3 kg. Weight at birth 2.2 kg. Breast and cow's milk mixtures to 10 months. Afterwards chiefly milkfoods. Unable to sit up, fat, very pale. Has had pneumonia and frequent bronchitis.

The haemoglobin increased after intra-abdominal vacuum-plasma injections in 40 days from 47-82 % and erythrocytes from 3.7-4.9 Mill. (highest 5.8 Mill.). The reticulocytes increased after the first injection to 3 %, but decreased slowly to 1 %.

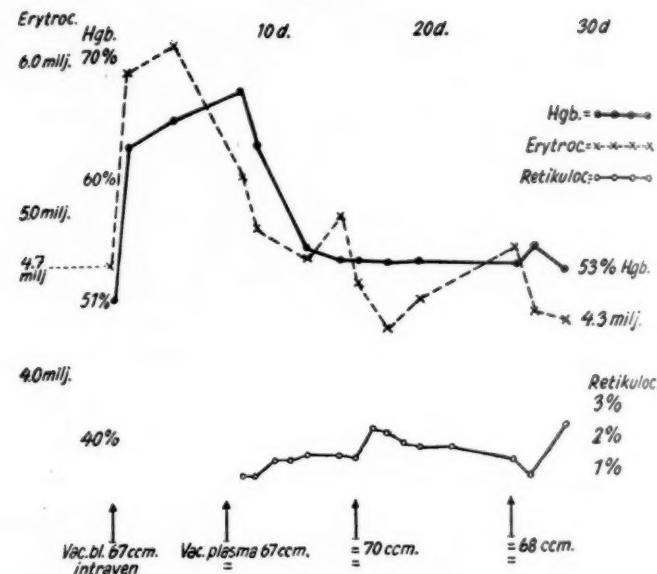


Fig. 3.

*Case 2 (Fig. 2).* Martti P. 11 months. Weight 8,4 kg. Weight at birth 2,3 kg. Premature. Cow's milk feeding. Has had infected haemangioma capitis. Frequent diarrhoea and fever. After three intravenous injections the haemoglobin increased in 30 days from 41-72 % and the erythrocytes from 3,7-5,1 Mill. Reticulocytes increased to 3,5 %.

*Case 3 (Fig. 3).* Paula R. 15 months. Weight 7,6 kg. Weight at birth 1,65 kg. Triplet. Cow's milk feeding. Frequent diarrhoea. Very pale. After the first intravenous injection haemoglobin increased from 51-71 % and erythrocytes from 4,7-5,8 Mill. The child began vomiting and developed diarrhoea. After one month the blood status was as before.

In an other of the triplets, who received the same injections, events took the same course.

In the third triplet, who as control received normal blood, events surprisingly enough again followed the same course.

Our cases are yet too few to allow any definite conclusion.

But in any case we can see that *in human vacuum-plasma these haematopoetins do exist and that in some cases of anaemic children after infections they are able to effect an increase of erythrocytes, haemoglobin and reticulocytes.* This without the help of the usual good antianaemic remedies, e. g., iron, liver, whole blood, etc.

That these haematopoetins will be produced in the blood *as well in general as in local anoxia* and as well "in vivo" as "in vitro" are shown by the following experiments of Bonsdorff.

If a *stasis* be made round a subject's limb and the normal circulation thus inhibited for 1-2 hours erythrocytes will increase the following day by half a million and remain at this level for 4-5 days.

Here opens a new perspective for treatment of anaemia. The old treatment by stasis (Bier), which had such good results in joint-diseases, is here explained anew and quite a new and wider field is presented it.

Our investigations are still going on. But I venture to present them to my Nothern colleagues in the hope that they will arouse interest in the whole question of anaemia in children, which is so important in these Nothern countries.

#### *Summary.*

*Plasma from deoxygenated blood contains so called haematopoetins, which produce increase of haemoglobin, erythrocytes and reticulocytes in severely anaemic children.*

Among 12 children treated intravenously or intra-abdominally three showed positive results.

These haematopoetins exist also in the plasma of children with polycythaemia and after *local stasis* they can also be developed due to anoxia.

*From the Children's Department, Rikshospitalet, Oslo.  
Head: Professor Leif Salomonsen.*

## PERNICIOUS ANEMIA IN CHILDHOOD

By  
ARNE NJA (Norway).  
*Author's abstract.*

In the hematologic literature it is not generally recognized that cases of so-called "genuine" pernicious anemia may occur in infancy. From America numerous cases of megaloblastic anemia have been described that are to be looked upon as symptomatic. In the Scandinavian literature, however, 6 cases of anemia in children have been reported that meet the requirements set up for the diagnosis of pernicious anemia in adults (Dedichen 1942, Jonsson 1945, Karlström & Nordenson 1945, Murray 1947, Jacobsen 1947, Edgren & Segerdahl 1948). Two similar cases have been reported from America (Peterson & Dunn 1946, Benjamin 1948).

In the Pediatric Department of the Rikshospital we have had occasion through a number of years to follow 5 patients suffering from this disease. One of them is the boy described by Dedichen in 1942; now he is 10 years old and has to keep on with the liver therapy.

In three of the other children the symptoms commenced at an age of 1½-2 years, and in one child at the age of 4 years. All these patients but one were boys. In all of them the disease was progressing in about the same way with increasing tiredness and pallor, anorexia, and marked impairment of the general condition. On examination of the patients in this clinic a considerable degree of hyperchromic anemia was ascertained (Hb 30-50 %), with a color index of up to 1.5. In most of these cases there was also a more or less pronounced leukopenia, together with moderate thrombopenia. In all the cases the bone marrow was found to be megalo-

*Table I. Essential Laboratory Data before and after Treatment with Folic Acid (Pt. No. 1) and Liver Extract (Pts. No. 2-3-4).*

Pat. No.	1		2		3		4	
	Before	After	Before	After	Before	After	Before	After
Hb % .....	50	98	40	89	29	88	38	80
R. b. c. .....	2.26	4.14	1.3	4	1.15	1.15	1.5	4.24
W. b. c. .....	6.400	7.100	8.000	12.000	3.000	9.600	2.400	5.100
Color index .....	1.15	1.21	1.5	1.1	1.26	1.01	1.26	0.95
Thrombocytes .....	159.000	71.000	Megalo- blastic	84.000	Megalo- blastic	50.000	Megalo- blastic	
Bone marrow .....	Hypop- lastic*)	Normo- blastic	HCl +	HCl -	HCl +	HCl -	HCl +	Normo- blastic
Ewald's test meal .....	HCl +	—	HCl +	HCl +	HCl +	HCl +	HCl +	
Histamine test .....	—	—	—	—	—	—	—	
Serum iron, γ % .....	183	90	229	46	287	73	196	95
Reticulocytes, max. per thousand .....	151	320	500	490				

\*) The bone marrow became megaloblastic also in this patient after the liver therapy had been discontinued for some months.

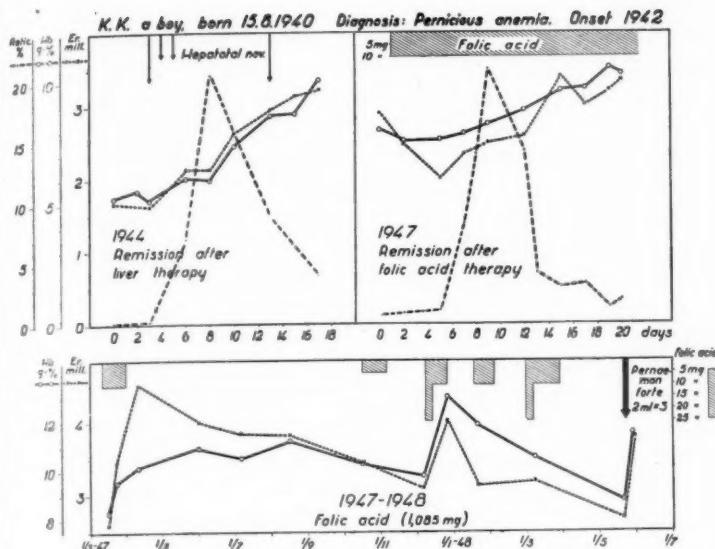
blastic. On treatment with injectable liver extract or with folic acid by mouth, perfectly normal blood values were obtained in all the cases, and at the same time the bone marrow became normoblastic. Under this treatment there was a very marked increase in reticulocytes, up to 500 per mille. In all the patients two or more relapses were ascertained when the treatment was discontinued. The relapses appeared when the children had received no treatment for  $\frac{1}{2}$ - $1\frac{1}{2}$  years. In one of the cases it was found necessary to give both liver and folic acid simultaneously in order to keep the blood values at a normal level. Halometry showed a somewhat increased diameter of the erythrocytes. The serum color was normal in all the patients. No sign of any kind of intestinal lesion was found in any of these patients, nor any nutritional deficiency. They all showed a constant proteinuria, without other signs of any kidney lesion. Histamine-refractory achilia did not occur in any of the patients (Table 1).

The author thought it was practical to establish that in early childhood a form of anemia occurs which clinically, hematologically, and in responds to treatment with liver and folic acid behaves like pernicious anemia in adults. Whether it is to be looked upon as identical with the latter is uncertain. Probably it represents a particular form of anemia, and in order to differentiate it from the variegated group of symptomatic megaloblastic anemias in childhood it was suggested to designate it as infantile pernicious anemia.

#### DISCUSSION

*Bo Vahlquist (Sweden).*

From the Norrtull Hospital some cases of pernicious anemia in children have been published in later years. In one of these treatment with folic acid gave initially prompt effect with reticulocyte crisis up to twenty per cent. After one year of intermittent treatment folic acid no longer gave complete restitution of the hemoglobin and erythrocyte values, and increasing anorexia and fatigue were noted. Liver treatment rapidly ameliorated the blood values and after a few days all subjective symptoms completely disappeared. Details are given in the Fig.



## NUTRITIONAL EXPERIMENTS WITH A NEW TYPE OF HUMANIZED COW'S MILK

By

MARY FALLESEN and ERIK OLSEN (Copenhagen, Denmark).

*Authors' abstract.*

The well-known difference between the stools from breast-fed infants and bottle-fed infants is taken by many authors to be due to bacterial factors, as they think that the acid-producing *Bac. bifidum* is found in practically pure culture in the feces of breast-fed infants while it is absent in bottle-fed infants, on which account the stools of the former become acid, the stools of the latter neutral.

On bacteriological examination of numerous samples of feces from both categories of infants, one of us (Olsen) found the number of *Bact. bifida* to be practically the same in breast-fed and bottle-fed infants, whereas *B. coli* and enterococci are a little more numerous in the latter. Furthermore, clostridia, coryne bacteria, and Veillonella are found in bottle-fed infants, whereas they are absent in breast-fed infants, owing to the low pH of the intestinal contents. When breast-fed infants commence to get a mixed diet, containing cow's milk, their stools become like those of bottle-fed infants with regard to pH, appearance, and smell. Also the bacteriological picture changes becoming the same as encountered in bottle-fed infants — with the exception that it takes a long time before clostridia turn up in the feces.

When bottle-fed infants are given mixed diet, no change takes place in the make-up of the bacterial flora or in the character of the feces.

Thus the total number of bacteria is greater in bottle-fed than in breast-fed infants; but, as all the more important groups of bacteria are acid-producing, the higher pH in the feces of bottle-fed infants cannot be due to these bacteria. Rather the opposite may be assumed to hold true, as these bacteria — like pathogenic bacteria — have a higher pH optimum and therefore thrive better in the less acid intestinal contents in bottle-fed infants.

Thus the difference between the feces of breast-fed and bottle-fed infants is more likely due to the difference in the chemical composition of mother's milk and cow's milk, and it proved possible by altering the composition of cow's milk so that chemically it resembled mother's milk as far as possible to obtain stools which quite resembled those of breast-fed infants with regard to pH, smell, and consistency.

*From the Children's Hospital at the University, Åbo.  
Head: Professor T. Salmi.*

## ON THE WATER, ELECTROLYTE, AND PROTEIN BALANCE IN ACUTE INFANTILE DYSPEPSIA

By  
**OLLE PALMBERG** (Finland).

*Author's abstract.*

On 230 infants, 1-12 months old, suffering from acute dyspepsia with intoxication, serial determinations were made of haemoglobin, erythrocytes, haematocrit value, plasma protein, plasma chlorine, and plasma alkali reserve.

By means of diagrams it was shown:

- 1) that a slight increase in the haemoconcentration occurs at any rate not infrequently even before we are able to observe any clinical signs of intoxication;
- 2) that an increase in the haemoglobin percentage and in the erythrocyte count, as signs of increased haemoconcentration, in more severe intoxication often are counterbalanced in part or even completely by a simultaneously appearing infectious-toxic anemia;
- 3) that an increased haemocrite value may just as well be a result of acidosis as a sign of increased haemoconcentration;
- 4) that water deficit of the infantile organism is not associated with a decrease in the plasma chlorine value and that it therefore is not evident from the latter;
- 5) that cases with no, or slight, clinical signs of intoxication sometimes show slight alkalosis, whereas acidosis dominates in more severe intoxication;
- 6) that an increase in the plasma protein percentage as sign of increased haemoconcentration is counterbalanced by a hunger hypoproteinemia, and by an increased toxic protein decom-

position, increasing in degree with the duration of the illness;

7) that the protein values are lowered markedly in deep intoxication, which might be explained by increased permeability of the capillary membrane and the leaking of the proteins into the tissues — in analogy with the findings in "surgical" shock.

These investigations were taken to indicate:

a) that the clinical picture of intoxication in acute infantile dyspepsia involves at any rate the following factors: increased haemoconcentration, disturbance of the acid-base equilibrium and, frequently, slight hyperchloremia in spite of probable hyposaluria; and

b) that the degree of dehydration and thus the quantitative water requirement are never deducible from these laboratory tests, as these are influenced by many mutually conflicting factors.

In answer to the question whether these tests then may be of any clinical value, whether they play any rôle in the estimation of the prognosis, and whether they may offer any suggestion about the therapy, a diagram was shown, from which it was evident:

1) that hypoproteinemia and hypochloremia are most dangerous;

2) that also marked hyperproteinemia and hyperchloremia aggravate the prognosis;

3) that acidosis is considerably more deleterious than alkalo-sis, which in its milder degrees is rather harmless.

4) that also other factors appear to play a rôle in the outcome of the disease, as exitus occurs not infrequently also in cases in which the protein, chlorine, and acid-base balance has been or been kept good throughout.

From the above the following conclusions are drawn:

1. The prognosis is chiefly, though not entirely, dependent upon the electrolyte and protein balance of the organism.

2. With our infusions we should try as quickly as possible to abolish a disturbance of the balance at its initial stage and avoid to disturb an existing balance. In doing this particular caution has to be exercised not to give an overdose of sodium

chloride or too great an overdose of infusion remedies rich in protein and bicarbonate.

In recapitulation it is to be emphasized that in order to be able to treat a case of acute infantile dyspepsia lege artis, we ought to follow closely the electrolyte and protein balance of the organism. Abnormal values that are of significance to the prognosis, however, are never encountered without clinical signs of intoxication. The water requirement is not evident from the laboratory tests performed. Consequently, the clinical picture presented by the child, the turgor of the skin and the weight curve decide when an infusion is indicated, and how much water should be supplied, and also whether laboratory analyses are necessary. These analyses thus serve as a qualitative guidance, and show which infusion remedy ought to be given in order to remedy a possible disturbance of the electrolyte and protein balance, simultaneously with the removal of the water deficit of the organism often even which substances we may venture to give without disturbing an existing balance.

#### DISCUSSION

*Per Selander (Sweden).*

The hemoglobin values given for a Finnish normal material are remarkably low, 63-70 %. In Sweden several investigations have been carried out (Magnusson, Faxén, Selander) in which the values keep at a 10 % higher level. During the war we had a fairly large number of Finnish infants in the hospital in whom we found no remarkably low hemoglobin values.

*Yngve Åkerrén (Sweden)*

points out that the high hemoglobin values observed as well as the low blood protein values in the severe cases of intoxication confirm the view that a state of shock plays an important rôle in pronounced intoxication. Shock therapy in the form of plasma or serum transfusion is of great value in these cases.

*Bo Vahlquist (Sweden).*

In the Norrtull Hospital we have made the same observation that the protein values in cases of severe diarrhea are often subnormal

in spite of pronounced clinical signs of dehydration. We thought it might be the result of interference with protein formation but possibly also a shock mechanism might be of importance as suggested by Dr. Akerrén.

The hematocrite values given for the normal material as 25 per cent were amazingly low. It is generally agreed that the average level at this age is about 35 per cent.

*A. Lichtenstein (Sweden)*

asks Dr. Palmberg whether the salt and water balance may be estimated without any potassium determination.

*From the Dronning Louise's Children's Hospital, Copenhagen.  
Head: Professor Oluf Andersen.*

## PERORAL GLUCOSE TREATMENT OF ACUTE DIARRHOEA IN INFANTS

### I. *Ketonemia in acute Gastro-Enteritis with a Special View to Glucose Treatment.\*)*

By

AAGE WARMING-LARSEN and E. O. ERREBO-KNUDSEN  
(Denmark).

*Authors' abstract.*

In a number of infants with acute dyspepsia we have studied the blood ketone concentration from the day of admission to hospital. In these infants, who by way of treatment were given the carrot powder diet commonly used, we found that in spite of the administration of bicarbonate, salt water and, in a number of cases, blood transfusions, the accumulation of ketone bodies reached slightly supernormal levels, although the concentrations in question were not so high as those observable in cases of praecoma and coma. While the normal blood ketone concentration is not more than about 5 mg. per cent, expressed in terms of  $\beta$ -hydroxybutyric acid, we found in our material values ranging from 10 to 20 mg. per cent and sometimes up to 30 mg. per cent. In a series of cases the ketonemic condition was counteracted by adding glucose to the carrot diet. In none of the cases examined by us this procedure proved harmful. On the contrary, it became possible by this means to prevent the occurrence of ketonemia. Although it is maintained from various quarters that acidotic conditions in infants are dangerous only in the most severe cases, it seems natural, however, to avoid the occurrence of hunger ketonemia when it is possible to do so without otherwise causing any harm. It is, therefore, recommended that

\* To be published in extenso in *Acta Pædiatrica*.

symptomatic dyspepsia in infants be treated by administration of carrot powder to which is added glucose in sufficient quantities to cover 10-15 per cent of the caloric requirement of the infant. This is achieved by adding to the ordinary carrot soup, containing 4 per cent of carrot powder, enough glucose to obtain a 2 per cent glucose solution. Consequently, if we assume that the amount of carrot soup ingested per 24 hours is approximately 1 litre, the result will be that the infant receives 70-80 calories in the form of glucose. Absorption of about one half to two thirds of this amount will suffice to cover 10 per cent of the caloric requirement.

*II. The Course of Epidemic Diarrhoea in the Newborn under Treatment with Carrot Soup (Idocaron\*) with and without Addition of Glucose\*\*).*

By  
AXEL BIERING (Denmark).

*Author's abstract.*

A comparison between two groups of 25 newborn infants each, treated for "epidemic diarrhoea in the newborn" with carrot soup, respectively carrot soup with an addition of 5 per cent glucose, shows a better weight curve for the latter group. The glucose had no unfavourable effect on the intestinal function. The deathrate and the occurrence of severe cerebral symptoms as well as the prognostically alarming edemas were the same in the two groups. The conclusion is that, in case of epidemic diarrhoea in the newborn, the strict inanition cure may be replaced by treatment with 5 per cent glucose in water or carrot soup. For several reasons the writer thinks that this ought to be done also in infectious gastroenteritis. It would be desirable to have this opinion checked by a similar comparative study.

\*) The solution of this preparation, which is manufactured by Ferrosan, Ltd., Copenhagen, contains about 1.1 per cent of fructose and 0.9 per cent of saccharose.

\*\*) To be published in extenso in *Acta Pædiatrica*.

## DISCUSSION

*Erik Gedda (Sweden).*

In 1927 I heard a lecture given by Pirquet on acute dyspepsia in which he warned against the tea-saccharine therapy commonly employed in general practice, which he wanted replaced by tea with refined sugar which he considered non-irritating because of its ready absorbability. If there already are nausea and choking it is advisable to commence with cold carbonated sugar water, a teaspoonful at a time. At least this ought to be easier for the children to take than carrot soup.

With this regimen I have not yet seen any intoxication among my patients. Of course, this may be a matter of good luck, but even so, it seems to imply a preventive measure against hunger acidosis. At any rate, this is a prophylactic question which I should like to hear my more experienced colleagues express themselves about.

*Per Selander (Sweden).*

In Kristiansstad, in the past 5-6 years, we have prescribed carrot soup in toxicosis and severe dyspepsia in infants and found it to be the sovereign remedy in such cases. But we have not had occasion to try it in epidemic diarrhea in the newborn. Carrot soup is no longer troublesome to make. Its preparation in a high-pressure boiler takes only 15 min.

*P. W. Bræstrup (Denmark).*

When physicians have been afraid to give carbohydrates in acute infantile diarrhea, no doubt their attitude has been greatly exaggerated, and it is good to hear that the administration of glucose is harmless.

Correspondingly good results have been obtained in my department in cases of acute diarrhea by giving the patients a preparation of carob-beans (locust-bean or St. John's bread) (Arobon, Nestlé), which contains over 50 % carbohydrate, a great part of which is added high-molecular starch. The therapeutic results obtained in this way are presented by Dr. Anna Frandsen at the congressional exhibition and, according to our experiences so far they are at least as good as those obtained with other forms of treatment of diarrhea. This account further shows that it is quite justifiable to make this treatment of brief duration, so that cow's milk may be added to the diet on the second or third day, after which the diet soon becomes adequate as to its caloric content.

*A. Lichtenstein (Sweden).*

In Crown Princess Lovisa's Childrens' Hospital we regularly employ administration of glucose. When severe vomiting prevents its administration by mouth, we give the glucose parenterally, often in form of intravenous drip of equal parts of saline and 5% glucose. There is also reason to point out the value of employing Ringer's solution — in order to supply not only sodium but also potassium and calcium.

*N. Malmberg (Sweden).*

It has been of the greatest interest to me to hear about the investigations reported here, as over 15 years ago I commenced employing administration of glucose at the initial treatment of enterocolitis in infants as well as in older children.

From a practical point of view it is of great importance to counteract the ketonuria. This is usually accompanied by apathy, loss of appetite and vomiting which preclude the oral administration of the therapeutic mixtures we would like to give the patients.

As to the serviceability of glucose in infectious enterocolitis — as is evident from my publications in 1934 — I have treated dysentery patients with apple diet plus glucose, with excellent results.

*Erik Frisell (Sweden).*

In treatment of the more severe forms of gastro-intestinal infections in infants and small children, when the patients are in a state of shock, and vomiting renders feeding by mouth impossible, we have employed the following technique for intravenous nutrition here in the Sachs Children's Hospital since 1945.

A flexible and blunt silver needle is introduced in the saphenous vein immediately above the medial malleolus and it is retained here throughout the critical phase of the disease. The child receives its nourishment through this needle, entirely or partially, depending on the intensity of the vomiting. Nutrient fluids are given by injection, and the amount may be dosed exactly according to the needs of the child. Thus we avoid completely the most frequent complication from intravenous dropwise instillation, namely: edema, due to excessive administration of water. The injections are given approximately every three hours (7 times daily) and each injection should take about 20 min. Analysis of the blood is carried out as often as required by the situation.

The following solutions are employed for the infusions: Aminosol-glucose solution, containing 3.3% amino acids (Aminosol) and 5% glucose; bicarbonate solution 1.3%; Darrow's solution, Ringer's solution, and glucose solution 5%.

The treatment begins with blood or plasma, given once or twice during the first 24 hours; on continuation of this measure, plasma should be avoided because of the risk of edema. The optimum dosage of Aminosol is 2 g. per kg. body weight. The other solutions are given according to the requirements. At each injection, penicillin is given through the needle, often also in injectable sulphonamide preparation, to combat the underlying infection and also to reduce the risk of secondary infection that may be brought about with this technique. (Additional blood transfusion is given if the blood values decrease or if the general condition of the patient is aggravated). Finally, heparin (0.1-0.2 ml. of a 5 % solution) is injected, so that the needle is always filled with this remedy between the injections.

In this way we have maintained intravenous nutrition for up to 7 days. Usually, for some reason or other, this regimen ceases to function a couple of days before. This applies in particular to the premature children because hitherto our smallest needles have not been able to stand the strain but have broken in the soldering. If continued intravenous nutrition is required a new needle is inserted in the other leg or in an arm.

To begin with, nothing is given by mouth or only a small amount of water. When the patient improves, carrot soup is given, which is tolerated well even by the smallest prematures (our smallest one weighed 1400 g.) and may be given with syringe and stomach tube if required. The salt content of the carrot soup (0.3 %) gives a certain retention of water, which in this case is very desirable. Later, a gradual change of nutrition to mother's milk or a suitable cow's milk mixture is made. Both of these are at first made less rich in fat by skimming.

A more detailed account of our experiences with this technique will be published in some other connection.

#### *V. Rantasalo (Finland).*

In the Epidemic Hospital in Helsinki, since 1941 we have used carrot soup in cases of enteritis. Over 1000 cases have been treated in this way and the results have been so good that gradually we have discarded all other methods of treatment. In the first two days the carrot soup is given in large doses, on the first day without sugar. After two days, at the latest, citrated milk is added in increasing doses. Under this treatment intoxication has been almost absent.

#### *Aage Warming-Larsen (Denmark).*

To Dr. Frisell: In children the demonstration of ketone bodies in the urine is a very gross method as the renal threshold for

ketone bodies is considerably higher in children than in adults.

To Dr. Friderichsen: As a matter of fact, the proportion between  $\beta$ -hydroxybutyric acid and the total ketone content changes in favor of the  $\beta$ -hydroxybutyric acid. This explains the difference in the curves obtained by Dr. Friderichsen and my curves.

*Axel Biering (Denmark).*

To Dr. Selander: We have no experiences with native carrot soup.

To Professor Lichtenstein: Idocaron contains potassium in the same concentration as in mother's milk.

To Dr. Friderichsen: The treated patients are the same as we have designated as "malignant gastro-enteritis", with a mortality over 20 %. I have preferred the international designation "epidemic diarrhea in the newborn".

*From the Pediatric Clinic at Norrtull's Sjukhus, Stockholm.  
Head: Professor A. Wallgren.*

## **EXPERIENCES WITH A SIMPLE CLINICAL METHOD FOR DETERMINATION OF THE METABOLISM IN INFANTS**

By  
**P. KARLBERG (Sweden).**

*Author's abstract.*

In the Norrtull Hospital in Stockholm a simple method has been worked out for determination of the metabolism in infants for practical clinical use (described by Karlberg & Lind in *Nordisk Medicin*, 1948). In order to reduce the cost of the apparatus and to make the technique as simple as possible and similar to the one employed for adults and older children, we have employed the Krogh spirometer in standard form. This is connected with an airtight chamber for the child and a circulation pump. The chamber is made of plexiglass, in the shape of a large cheese cover, standing on a plate with a water-filled groove. The pump is of the Cellow type. The volume of the system is about 50 l. (Fig. 1.)

Thus the principle of the method is indirect calorimetry with a closed respiratory system in which the carbondioxide is absorbed. The oxygen consumption of the child is measured by registration of the decrease in the volume of the system. The apparatus is controlled by means of the alcohol test.

By following the temperature and humidity in a great many examinations it could be shown that balance in the system appears 30-50 min. after the commencement of the examination. After this, the examination continues for 30 min. and the oxygen consumption of the child (= decrease in the volume of the system) is measured for this period. Any possible movements of the child are observed and recorded by the nurse.

In this way, about 500 examinations were performed on

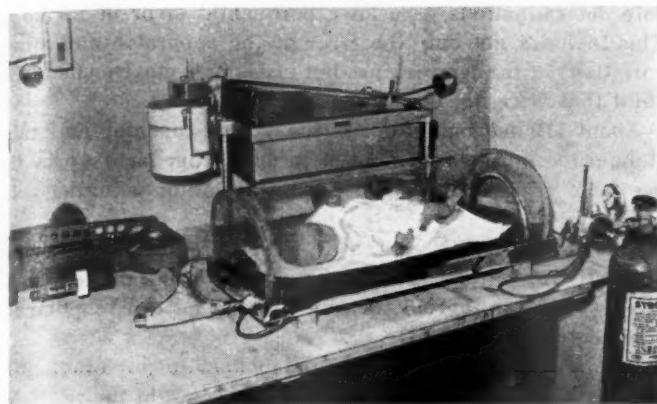


Fig. 1.

infants, from new-born up to the age of about 2 years and suitable standard conditions were studied.

Naturally the child should be lying quietly. Even relatively slight movements give a distinctly registrable increase in the oxygen consumption. The younger infants usually sleep spontaneously after they have been in the chamber for 10-15 min., but often this does not apply to the older infants. Therefore, as a rule, the latter are given immediately before the examination a small dose of a barbituric acid preparation (5-15 cg. enhexymal, according to the weight of the child). It takes more than twice this dosage to produce a noticeable decrease in the oxygen consumption.

The examinations have been performed at various times after the meal. No increase in the oxygen consumption was found with an interval of 3 hours or more.

Several children were examined at an air temperature of 26-29° and showed then a slight decrease in the oxygen consumption. But an increase or decrease of 1-2° in the ordinary room temperature had no noticeable effect on the oxygen consumption. In view of this, a special apparatus for regulation of the temperature was not considered required.

Statistical treatment of the differences in about 130 dupli-

cate determinations gave an experimental error of  $\pm$  3.6 %. This includes not only the error of the apparatus and minor variations in the temperature but also small movements of the child that were not observed.

About 110 determinations of the oxygen consumption under standard conditions on normal infants from birth up to the age of 2 years have shown good correlation with the body weight.

Four infants with untreated hypothyroidism gave values distinctly lower than those obtained for normal infants, 30-40 % lower. Under thyroid therapy the oxygen consumption increased to normal level.

Determination of the basal metabolism in an infant after this method takes about one hour. On account of the relatively low experimental error, and because the patient need not get accustomed to this form of examination, as a rule, it is not necessary to repeat it — in contrast to the examination of older children and adults, on whom at least 2 determinations have to be performed, each lasting half an hour. The examination can readily be managed by one person, and since the technique here differs but slightly from the technique usually employed for older children and adults, it can be performed by a laboratory technician trained in the care of infants.

#### DISCUSSION

*Erik Malm (Finland).*

With reference to Dr. Karlberg's lecture I should like to mention some experiments carried out in the Children's Hospital in Helsingfors.

In studies on the metabolism of prematures Räihä has previously demonstrated that the variations in the oxygen consumption are considerably greater than the variations in the carbondioxide output. He also ascertained that the values for the respiratory quotient varied more widely the smaller the premature examined was. Räihä's experiments lasted 3-4 hours and the oxygen consumption was registered at intervals of half an hour.

In order to be able to follow the gas exchange during a shorter period, we have constructed a mask combined with a valve and a gas-collecting bag (Fig. 1).

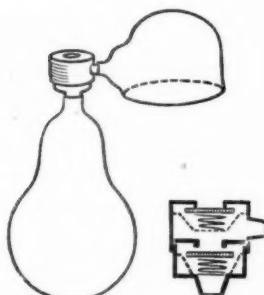


Fig. 1.

Under suitable conditions this apparatus may be employed for determination of the metabolism after the same principle as the Douglas bag. The air bags are shifted and the time is recorded for each bag. A part of the contents is analyzed for carbondioxide and oxygen (Haldane), and the rest is forced through a gas meter, and its volume is read.

Surprisingly many prematures stand the mask well and sleep while the experiment goes on. In one case the premature had the mask on for 1 hour 40 min.

For illustration of the results thus obtained I wish to show the following graph (Fig. 2).

This experiment lasted 40 min., during which period 11 samples were collected during a total period of 31 min., while it took

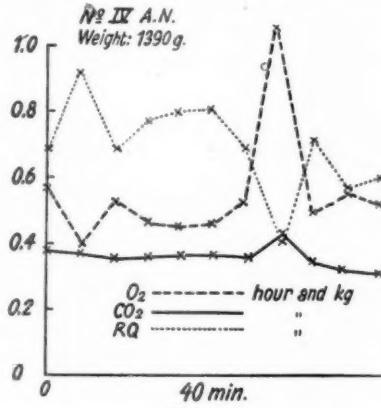


Fig. 2.

altogether 9 min. to change the bags. Here we see a curve of the same character as those published previously by Räihä, namely abrupt and pronounced deflections on the oxygen consumption curve and the curve for the respiratory quotient, together with a more stable curve for the carbondioxide production.

At present, the small size of the material allows of no detailed analysis of the results obtained.

*C. E. Räihä (Finland).*

I wish to congratulate Dr. Karlberg for the elegant way in which he has solved the problem to work out a practically serviceable apparatus for metabolism determination on infants.

To Dr. Malm's experiment I wish to add that the valve has a dead space which Malm has reduced by filling it and therefore inspiratory air is inhaled directly through a valve placed in the mask.

From The Pediatric Clinic at Kronprinsessan Lovisa's Children's Hospital, Stockholm.  
Head: Professor A. Lichtenstein.

## THE PROGNOSIS IN OBESITY IN CHILDREN

By

HANS-OLOF MOSSBERG (Sweden).

*Author's abstract.*

In order to throw further light on the prognosis of obesity in children a follow-up investigation of the obesity materials from all the children's hospitals of Stockholm was made at Kronprinsessan Lovisa's Children's Hospital. About 200 of the followed-up children may be considered as *untreated* and the condition of these children during growth was specially discussed.

The investigation showed that cases of *infantile obesity* as a rule should be considered as physiological extremes in which the obesity in the majority of the cases regresses during development. Cases with  $> 1$  obese individual in the "family" became generally more obese during growth than did cases with 0-1 obese individual in the "family". The result seems to show that the prognosis of obesity at the age of 0-2 years to a certain extent may be predicted from the number of obese individuals in the "family".

The obesity in 153 cases of *diffuse obesity* and *Fröhlich-like obesity* increases anew after a marked spontaneously decrease during and after puberty, and frequently in adulthood ( $\geq 20$  years, average age of 53 cases was  $24 \frac{9}{12}$  years) again attains a greater or lesser development. There was no prognostical difference between the two types of obesity. The prognosis in adulthood thus is rather variable, and for the obese girls considerably poorer than for the obese boys. Those girls who at hospitalization belonged to the more obese group appeared to have the poorest prognosis, while the less obese boys appeared to have the best prognosis.

The knowledge of the number of cases of obesity in the "family" seems to be of value in the evaluation of the prognosis for the obese patient with diffuse obesity. Another factor of importance for the degree of overweight, regardless of the age of the patient, is — as is well known — the degree of luxurious eating.

The typical fat distribution of cases of Fröhlich-like obesity seems in adulthood to regress gradually or to attain a more diffuse distribution. The puberal and genital development in these cases showed no difference in comparison with the development in cases with diffuse obesity. This is in agreement with the opinion that the hypogenitalism is apparent only and is not based upon a real hypoplasia of the genitals. The earlier strictly maintained difference between cases of Fröhlich-like obesity and diffuse obesity seems not to be justified.

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Mossberg, H.-O.: *Acta Paediat.* Vol. XXXV, Suppl. II, 1948.

From the Dronning Louise's Children's Hospital, Copenhagen.

Head: Professor Oluf Andersen.

and the Pediatric Dep. University Clinic at Rigshospitalet,  
Copenhagen.

Head: Professor P. Plum.

## BASAL METABOLISM IN OBESE CHILDREN

By

K. BIERING-SØRENSEN (Denmark).

*Author's abstract.*

The basal metabolism was determined on 178 children with adipositas, 83 boys and 95 girls. The children were from 3-15 years old, and their weight varied between 114 % and 198 % of the normal weight, in two thirds of the children between

*Metabolism in relation to weight*

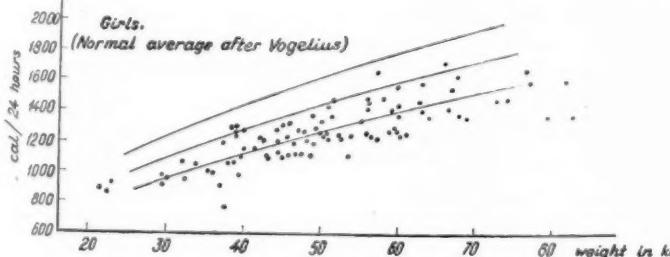
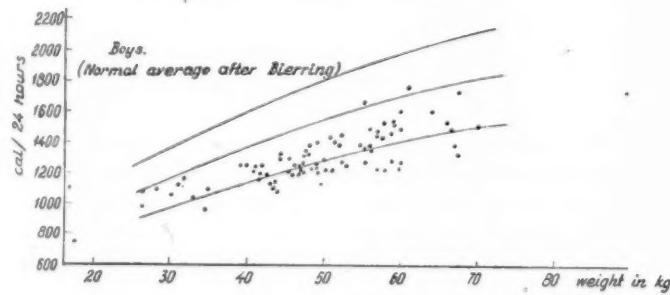


Fig. 1.

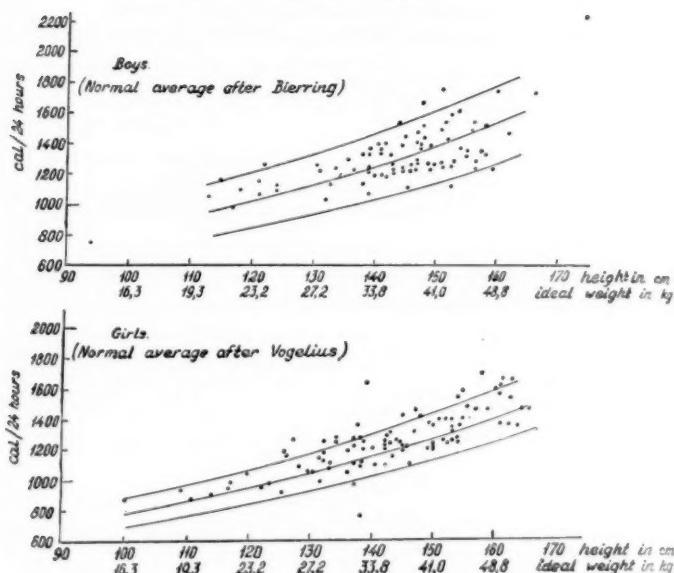
*Metabolism in relation to height.*

Fig. 2.

120 % and 150 %. Apart from a single case of myxedema, none of these children presented any sign of thyroid insufficiency or any other endocrine affection. The development of the nuclei of ossification and the height of the children were normal for their age, and puberty commenced at normal time in most of the cases.

The rate of metabolism was determined under the usual standard conditions immediately after admission to the hospital (Dronning Louise's Children's Hospital and the Pediatric Dep. at Rigshospitalet), before the children were placed on any reducing diet. In order to obtain basal values, 4-8 measurements were performed on each patient, and the calculation was carried out on the basis of several metabolisms when the oxygen intake per min. kept constant in several successive determinations.

Fig. 1 shows the relation between the basal metabolism and

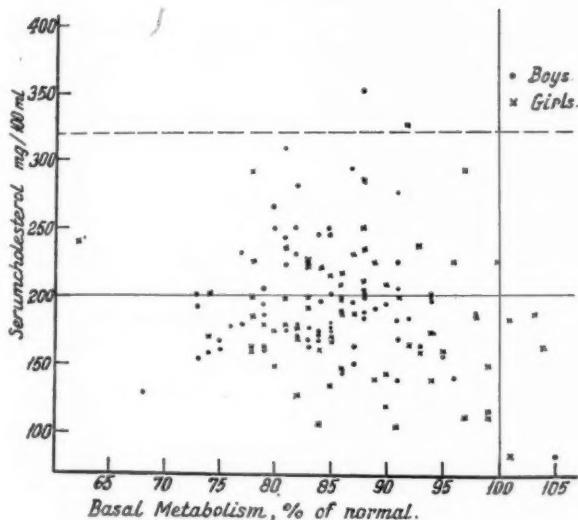


Fig. 3.

the weight of the child. Further, in this graph the normal curves have been inserted, too (for the girls after Vogelius, for the boys after Bjerring) with the limits given by these authors. It will be noticed that in the obese children the caloric production on an average lies about 15 % below the calculated caloric production for normal children of the same weight.

Fig. 2 shows that the caloric production in relation to the height (i. e., the ideal weight) comes very near the normal values given by Vogelius and Bjerring. On both curves the rates of metabolism are distributed evenly, with a normal dispersion to both sides. Only one patient, with clinical myxedema, showed a considerably lower caloric production.

Even though the normal curves here employed are to be accepted only with reservation, being calculated on children of normal proportions, the deviations in Fig. 1 still appear so pronounced that it seems justified to speak of a lowered caloric production per weight unit in obese children in relation to normal children. On 143 of these children also the cholesterol content of the blood was determined. It was found to be

normal, without relation to the rates of metabolism. This finding together with the normal physical and mental development of the children go against a lowered thyroid function as the cause of the decreased metabolism observed.

#### DISCUSSION

*Hans-Olof Mossberg (Sweden).*

The standard rates of metabolism for 319 children in the Stockholm's Children's Hospital are compared to the normal standard rates given by Lewis *et al.* in 1940. The total standard metabolism showed higher values than normal — on comparison with the chronologic age as well as with the height age.

On comparison with the various Lewis standards the best agreement is obtained — as compared to the standards for total body surface — and with the same dispersion ( $\pm 18\%$ ) as normally.

The results in relation to overweight are the same as obtained by Biering-Sørensen, on which account they will not be reported here (see *Acta paediat.* Vol. XXXV, Suppl. II).

The low values in relation to the weight standard may mean that the proportion between active and inactive tissues in the body through the presence of the large amount of adipose tissue has shifted in the inactive direction.

It will be of interest to collect a respiratory metabolism material of markedly thin children in which way we perhaps might find the respiratory metabolism values lying at the upper limit for the normal rate.

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From *The Lying-in Dep. B. at Rigshospitalet, Copenhagen.*  
Head: Professor E. Brandstrup.

## THE BLOOD SUGAR LEVEL UNDER STANDARD CONDITIONS DURING THE FIRST DAY OF LIFE IN CHIL- DREN OF DIABETIC AND NORMAL MOTHERS\*)

By

JØRGEN PEDERSEN (Denmark).

*Author's abstract.*

These studies were carried out in the Lying-in Dep. B of the Rigshospital in Copenhagen, comprising 22 children of diabetic mothers, 19 children of normal mothers. During the first 24 hours after birth the children were lying quietly, without receiving any food or water. On each child, on an average 6 blood sugar determinations after the Hagedorn-Jensen method were made in the first 24 hours. Thus the children were kept under uniform and basal conditions.

### *Conclusions:*

1. Children of diabetics as well as the children of normal mothers can do without food or water during the first 24 hours without presenting any clinical symptoms.
2. Very low blood sugar values, 20-30 mg. % are seen in children of normal women as well as of diabetics without presenting any other evidence of hypoglycemia. The low values are more frequent in children of diabetics than in children of normal mothers.
3. Attacks of cyanosis are not correlated to the blood sugar values obtained in the children.
4. The average blood sugar curve for the first day of life is fundamentally the same in the children of normal mothers and of diabetics. It forms a plateau, which for both groups

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\*) To be published in extenso elsewhere.

is rather low (about 60-70 mg. %). It is a little lower for children of diabetics than for children of normal mothers.

5. There is correlation between the blood sugar value of the mother at the time of parturition and the average blood sugar concentration in the child kept under standard conditions during the first 24 hours of life.

#### DISCUSSION

*Jørgen Pedersen (Denmark).*

The relation between the severity of the maternal diabetes and the blood sugar level of the child has not yet been worked out completely. We are able to confirm the findings reported by P. White insofar as we, too, find the serum gonadotropin concentration to be higher in diabetics and toxemics than in normal pregnant women. But we have not tried the treatment employed by White, with large doses of progesterone and estrone, as, for various reasons, it does not seem well motivated.

*From the Lying-in Dep. B. at Rigshospitalet.*

*Head: Professor E. Brandstrup,*

*and from the Pediatric Dep. at the Sundby Hospital, Copenhagen.*

*Head: C. Friderichsen, M. D.*

## FOLLOW-UP EXAMINATION OF CHILDREN OF DIABETIC MOTHERS\*)

By

JØRGEN PEDERSEN and ANNIE SCHONDEL (Denmark).

*Authors' abstract.*

Prior to the introduction of the insulin therapy pregnancy was seen but seldom in diabetics, and most often it terminated in abortion. Whenever the pregnancy went on to term the mortality was high both for the mothers and for the children. After the introduction of insulin therapy the fertility among diabetics has increased, and the number of diabetics in the age class of childbearing is rising. At the same time the mortality from diabetes for the mothers has fallen considerably, but the incidence of toxemia of pregnancy and pathological deliveries is strikingly high among diabetics. The fetal lethality, on the other hand, is still high. As the delivery is often difficult, and the children are often debile one might imagine that the *survivors* might be encumbered with permanent sequelae. Therefore we thought it might prove of interest to carry out some follow-up studies on children of diabetic mothers — the more so as similar investigations appear not to have been performed before.

In the Lying-in Dep. at Rigshospitalet in the period of 1926-1947 altogether 152 diabetics gave birth to 207 children weighing over 600 g. Of this total, 77 = 38 % died before birth, during delivery, or just after birth; 130 were discharged alive. For our follow-up examination 109 children were picked out who were living in Copenhagen or its suburbs. Four of

\*) to be published in extenso elsewhere.

these children had died, 3 from intercurrent diseases, and in one the death resulted from microcephalia. So far, we have not been able to get in touch with 18 of these children; the remaining 87, 52 girls and 35 boys, were examined. Of these children  $\frac{1}{3}$  had been born more than 2 weeks before term; yet,  $\frac{5}{6}$  of the children weighed over 3000 g. at birth. There were more anomalies at birth and in the neonatal period than normally. Thus, nearly  $\frac{1}{2}$  of these children had been markedly asphyxiated at birth, and about  $\frac{1}{4}$  of the children showed signs of cyanosis in the first week of life. At the follow-up examination 74 of the children were between 6 months and 8 years old, and only 13 were between 8 and 15 years, which shows the increasing frequency of childbirth in diabetics.

Among the living children 4 pathological cases were found, namely:

- 1) a girl of 18 months with pronounced congenital heart lesion;
- 2) a girl,  $4\frac{1}{2}$  years old, with a severe degree of Little's disease and oligophrenia;
- 3) a girl, 6 years old, with oligophrenia;
- 4) a boy, 5 years old, with diabetes mellitus.

Of the total 91 children examined 86 (including 3 who had died of intercurrent diseases) had developed perfectly normally, mentally and physically, so that the prognosis appears to be fairly good for children of diabetics that survive the neonatal period. (*The follow-up examinations will be continued.*)

## DISCUSSION

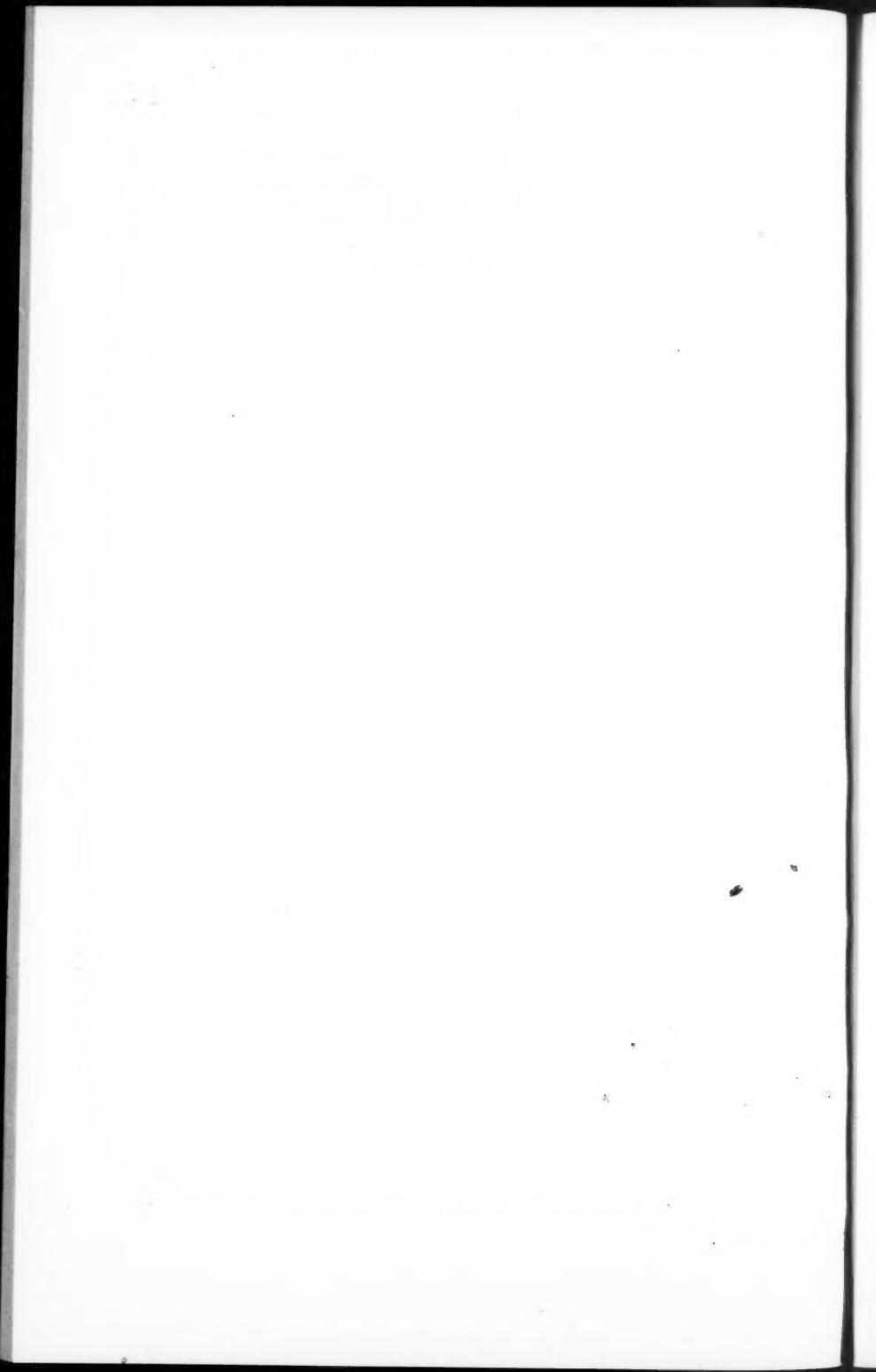
### A. Lichtenstein (Sweden).

I wish to thank Dr. Schondel and Dr. Pedersen for their interesting lectures. Also I have for several years been interested in the fate of children of diabetic mothers. We receive them in the Children's Hospital immediately after their birth. Generally we treat them with oxygen and glucose, even though the hypoglycemia is not decisive of the course of the individual case. In this I quite agree with Dr. Pedersen. A lethal outcome may be observed at a

normal or even very high blood sugar level. Dr. Pedersen said something about obesity in these children. Personally I am rather inclined to think that their overweight may be due to edema.

I should like to ask Dr. Pedersen whether he has worked up his material with regard to the degree of the diabetes of the mothers and their treatment with insulin. I think this is necessary if we are to correlate the blood sugar of the child with that of the mother.

Finally I wish to emphasize that I do not think that the intensive hormonal therapy during pregnancy advocated by the Joslin school has yielded convincing results. Our case mortality keeps at about the same level without hormonal therapy as has been obtained in Boston by hormonal therapy, i. e. about 20 %. I would like to ask Dr. Pedersen whether you have commenced giving hormonal treatment to pregnant diabetics here in Copenhagen.



## **SECTION VI**

**MONDAY, AUGUST 16.**

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## A DIPHTHERIC MILK EPIDEMIC IN HELSINKI

By

VILJO RANTASALO (Helsinki, Finland).

*Author's abstract.*

An epidemic of diphtheria due to infected milk broke out in Helsinki in the beginning of January 1948. 105 cases.

The throat symptoms were relatively severe, but the risk of heart complications was slight. None of the patients died.

The diphtheria bacillus belonged to the mitis group, showing marked toxicity in the test animals (guinea-pigs and rabbits).

SOME BACTERIOLOGICAL ASPECTS CONCERNING  
INFECTIONS OF THE UPPER RESPIRATORY PASSAGES  
IN INFANTS

By

GUNNEL MELIN (Stockholm, Sweden).

*Author's abstract.*

Studies concerning the etiology of acute infections of the upper respiratory tract in infants and children were carried out in some day nurseries in Stockholm during 1946-1948. In these nurseries the clinical aspects of the children were followed very closely through the daily health control by the physician and nurse attached to the respective nurseries, making it possible to correlate the bacteriological findings with the clinical features.

The bacteriological material comprises chiefly nose and throat swabs, besides local foci of infection. The swabs were taken twice a month as a routine measure and, in addition, whenever an infection of the upper respiratory passages appeared. Further, the antistreptolysin titer, antistaphylococcal titer and specific agglutination titer for pneumococci were controlled every month.

The relative frequency of primarily bacterial infections of the air passages is considerably higher in the present material than in American materials of adults. It may be that the bacteria play a relatively greater rôle — and viruses a relatively minor rôle — as etiological factors in children than in adults.

Indeed, the faecal and nasal flora is found to differ in its composition in children of different age-classes. From American, British and Scandinavian investigations we know that during the first weeks of life the faecal and nasal flora is dominated by pathogenic strains of *Staphylococcus aureus*.

The day nursery material shows that older infants and

children at the younger pre-school age chiefly harbor pneumococci in their upper air passages. It has also been possible to a considerable extent to show that these bacteria are of etiologic significance to the appearance of protracted rhinitis, otitis and pneumonia. The types of pneumococci occurring in these children are entirely different from those encountered in adults in Stockholm. The most common infantile types are: 6, 7, 11, 14, 19, and 23.  $\beta$ -Streptococci occur but exceptionally in the youngest children — and then as a rule only in a single culture and not in connection with any morbid condition. In the rare instances where  $\beta$ -streptococci have given rise to some disease in the younger children, however, the anti-streptolysin titer has reached just as high values as seen in older children.

From the age of 4 years the  $\beta$ -streptococci occur more frequently in the children, and now they often give rise to infections with fever and, later, increased antibody titers. The pneumococci still occur to a great extent, but now they appear to be of less etiological significance than in the younger children.

Staphylococci occur to about the same extent. In children over 3 months they are only of minor etiological significance.

Hemophilus bacteria and Gram-negative cocci have been found only in a few cases, and apparently they have only seldom been of etiological significance.

The nursery children have very protracted infectious lesions with frequent new attacks of illness. It has been possible to demonstrate that these relapses often have been due to other types of infecting bacteria.

The results here presented constitute merely the first beginning of a study of the etiology of the acute infections of the respiratory passages in children. If appears, however, as if these infections not only differ in their clinical course but also, in some degree, differ in their etiology from similar infections in adults. Insofar as this proves to be the case, it will be of importance to our prophylactic and therapeutic measures.

*From the Pediatric Dep. at the Copenhagen County Hospital,  
Hellerup, Denmark.*

*Head: P. W. Bræstrup, M. D.*

## ACUTE OBTURATIVE LARYNGO-TRACHEOBRONCHITIS

By  
P. W. BRÆSTRUP (Denmark).

*Author's abstract.*

Obturating malignant laryngo-tracheobronchitis is an acute infection taking a fulminant course, partly with pronounced general intoxication, partly with more or less complete occlusion of the air passages by tenacious secretion, which often is the direct cause of death from suffocation.

The disease is well described in text-books, especially American, and several cases have been reported also in the Scandinavian literature (e. g. Boysen & Boysen, 1943; Arnesen and collaborators, 1947; Söderberg, 1947). One gets the impression that the disease occurs endemically and periodically, but in most cases in the Scandinavian countries it appears to have been given but slight attention, and there can be no doubt that it has been considerably more frequent than indicated by the cases recorded.

In our department, within about 2½ years, among 2300 patients admitted there have been 18 unquestionable and 10 dubious cases of this disease with a total of 17 deaths.

*18 Unquestionable cases (6 girls and 12 boys) among 2314 admissions in 1946-48.*

	cases	died
1946 .....	5	5
1947 .....	4	3
Jan.-May 1948 .....	9	5 (4 tracheotomies, 2 died)
Total .....	18	13 = about 70 % lethality.

*6 girls — 12 boys:*

Age	cases	died
2- 5 months .....	4	3 (2½ months, recovered after tracheotomy)
6-11 > .....	5	4
1- 2 years .....	6	5
over 2 years .....	3	1
<b>Duration before admission:</b>		<b>cases</b>
under 24 hrs. ....		15
24-48 hrs. ....		3

*Symptoms:*

Preceding: <i>Catarrhalia</i> (including 2 dubious) .....	15
<i>Acute high febrilia + distinct exhaustion</i> .....	18
<i>Respiratory difficulty (stridor, "croup" or "asthma")</i> .....	8 (9)
<i>Distinct laryngo-tracheal secretion (rattling, etc.)</i> .....	12
<i>Attacks of suffocation</i> .....	10
<i>Absence of coughing reflex</i> .....	7
<i>Acidosis, plasma bicarbonate (milli-equiv.)</i>	
> 20 .....	0
20-16 .....	4
15-10 .....	3
10 .....	1 (2)
(Not examined .....	10)

*Duration from admission to death in 13 fatal cases:*

Dead on admission .....	2
Died within 0- 4 hrs. ....	3
»     »     5- 9 » .....	5
»     »     9-24 » .....	1
»     »     24-48 » .....	2
Total .....	13

Age, sex, symptoms and duration of illness are given into the schematic survey of the 18 unquestionable cases.

Bacteriological examinations have nearly always turned out negative (pneumococci in 4 cases, hemolytic streptococci in 1, Pfeiffer bacilli in 1 case.)

#### *Treatment.*

*Quiet* — continuous watch — sedatives.

*Sulfathiazole* ("massive": on admission 30 eg./kg. body weight, repeated after 6-8 hours).

*Penicillin* (30,000-80,000 I. U.  $\times$  4).

*Streptomycin* (100 mg. per kg. per 24 hours, in 6 doses).

*Tracheotomy* (regardless of symptoms of stenosis) suction and local treatment (instillation of penicillin).

*Steam* (but room-temperature not over 22-23° C.).

*Oxygen* (possible oxygen tent).

*Head low* — lying on the stomach.

*Bicarbonate* (also in absence of acidosis; alkalinization loosens the secretion).

*Serum* (Pfeiffer B, possible on suspicion).

*Vitamin A.*

The treatment is outlined in the schematic survey above. Quiet and tracheotomy are the two most important points. These children must be kept in complete rest and quiet, as even otherwise insignificant intervention or examination may give rise to catastrophic attacks of suffocation. Therefore, only the absolutely necessary treatment and examination are to be employed and, as far as possible, all should be done in one seance.

Tracheotomy has saved the life of many of these patients, making suction of the secretion possible. The operation must *not* be postponed till the appearance of dangerous symptoms of stenosis — and signs of stenosis may be completely absent in fatal cases — but is to be performed as soon as the diagnosis is made.

Alkalization (bicarbonate given by mouth and intravenously) and rehydration may be of decisive value by loosening the secretion.

## DISCUSSION

*Lennart Hesselvik (Sweden).*

In recent years the employment of married women in the industry has been increasing markedly, and — parallel with this — there have been increasing difficulties in obtaining help in the households. In several places this fact has given rise to a considerable increase in the number of institutions for collective care of the children.

The hygienic problems associated with this trend of social development have attracted great interest in various places, especially in England in connection with the "war-time day nurseries" instituted in that country.

As just mentioned by Dr. Melin, in the last couple of years, studies have been carried out on the state of health among children in day nurseries in Stockholm, focused in particular on the catarrhal infections of respiratory passages, which play a considerable rôle in this connection.

As a supplement to the account given by Dr. Melin I wish briefly to point out some clinic-statistical conclusions that may be drawn from the first part of that investigation.

The purpose of this work was to get a reliable idea about the degree and extent of the morbidity among the children in a day nursery conducted after the usual principles and, thus, where no particular measures were employed for the prevention of infections.

The examination period covered 8 months, October 1946-May 1947. About 70 children, attending this day nursery, were submitted to continuous observation for the appearance of signs of infections such as fever, coryza, cough, pharyngitis, otitis, etc. At the same time about 70 children attending a kindergarten connected with the institution were under exactly the same form of observation. The same applies to control material of 134 children who were cared for in their respective homes exclusively — but selected so that in other respects they corresponded to the institution children as far as possible. In this selection of comparable control groups, regard was paid not only to the age and sex of the children but also to the hygienic, social and economical factors that conceivably might be of significance to the outcome.

The possibilities for equally efficient observations on the controls and on the institution material — as well as for obtaining a representative control material — were very good as the investigation could take place on an island within the city of Stockholm, on which practically all the children had their homes, and where the structure of the population was relatively uniform.

The observations were largely made by visiting the homes — by a physician in nearly 600 cases, by a nurse in nearly 700 cases.

Coryza, fever and otitis among institutional children and controls during the whole observation period.

Groups A—D

Boys

relative values

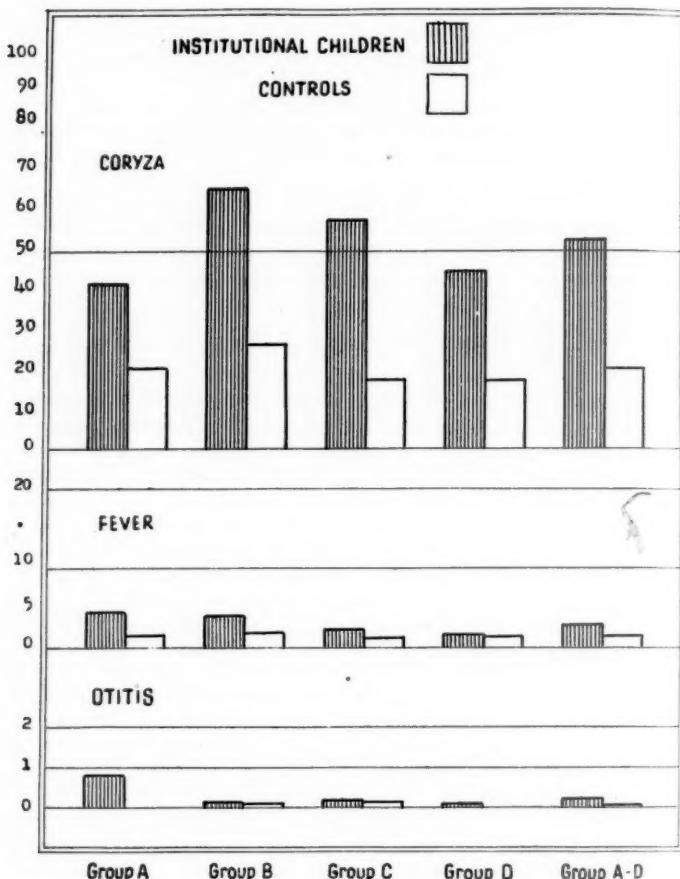


Fig. 1 a.

Coryza, fever and otitis among institutional children and controls during the whole observation period.

Groups A—D

Girls

relative values

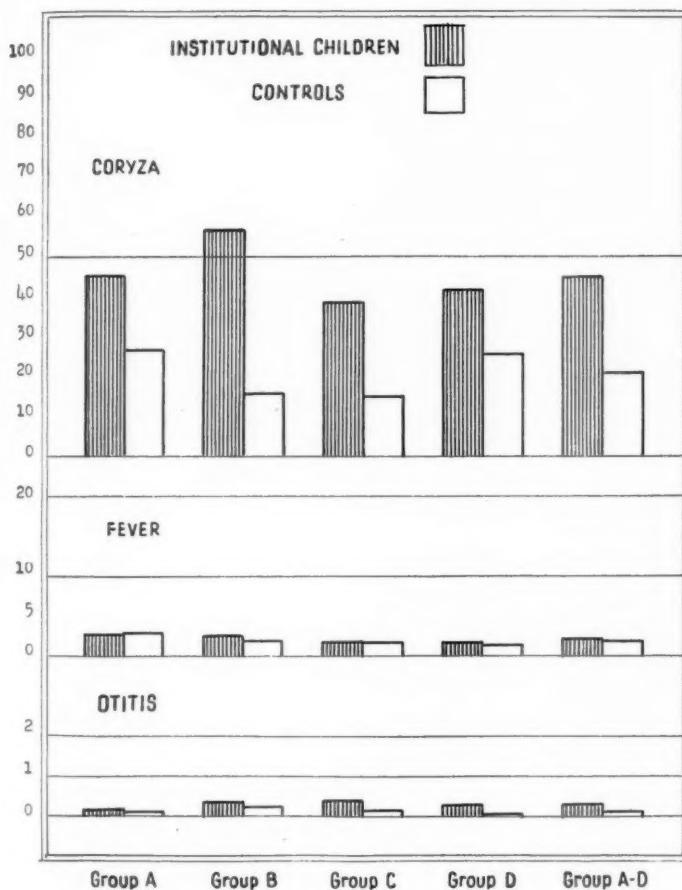


Fig. 1 b.

Coryza, fever and otitis among institutional children and controls during the whole observation period.

Groups E—H

Boys

relative values

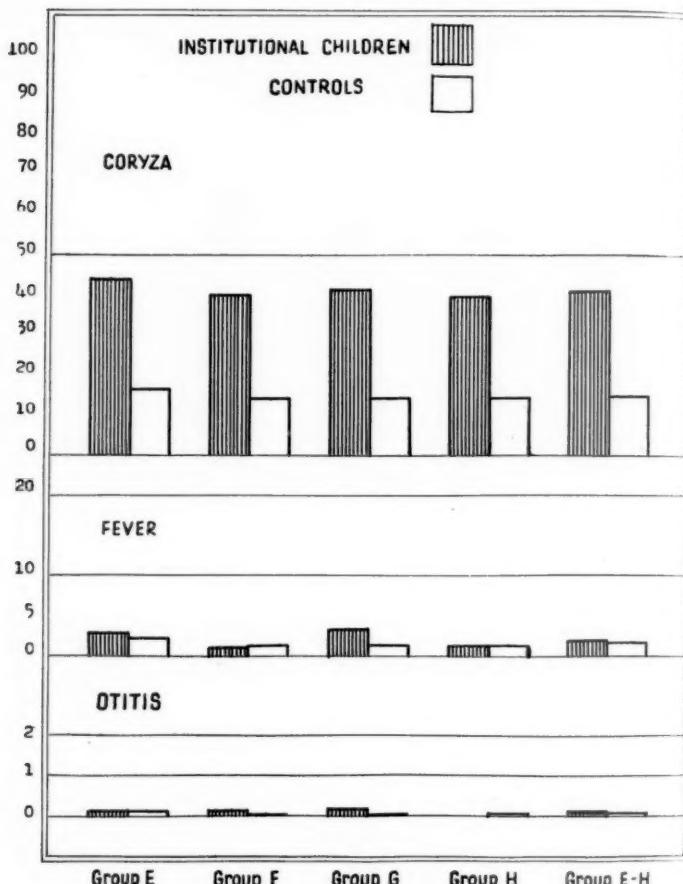


Fig. 2 a.

Coryza, fever and otitis among institutional children and controls during the whole observation period.

Groups E—H

Girls

relative values

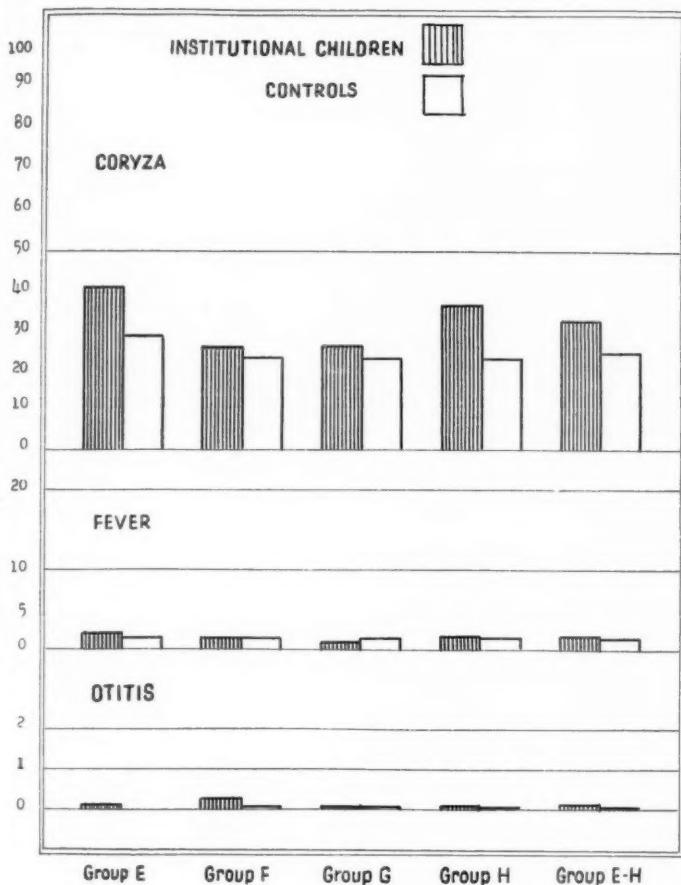


Fig. 2 b.

## Weight of children in different age-classes.

Boys

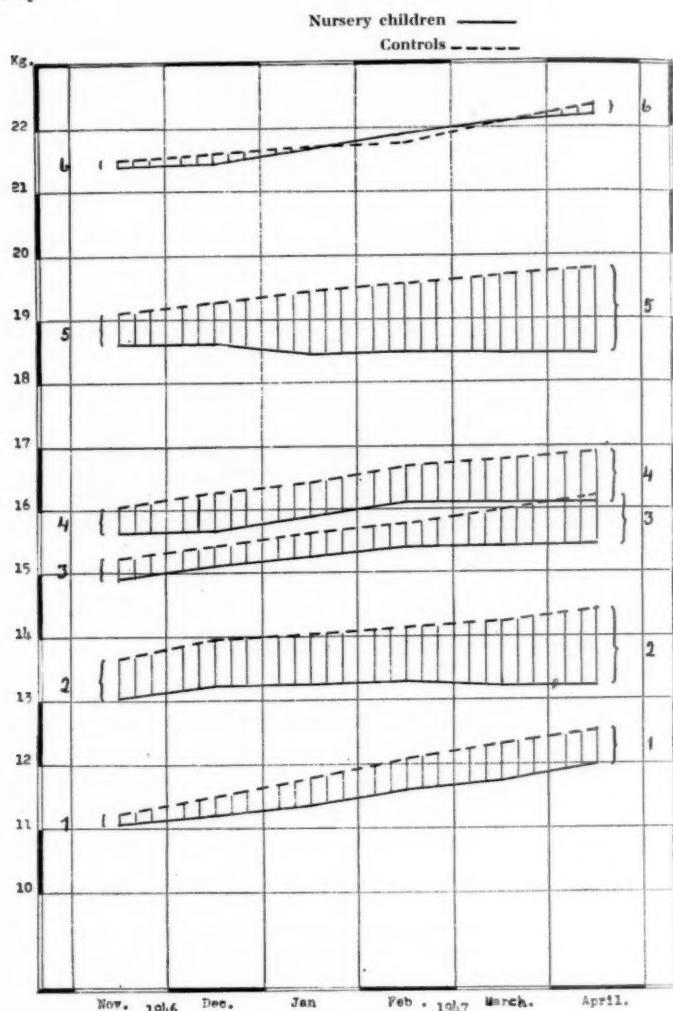


Fig. 3 a.

## Weight of children in different age-classes.

Girls

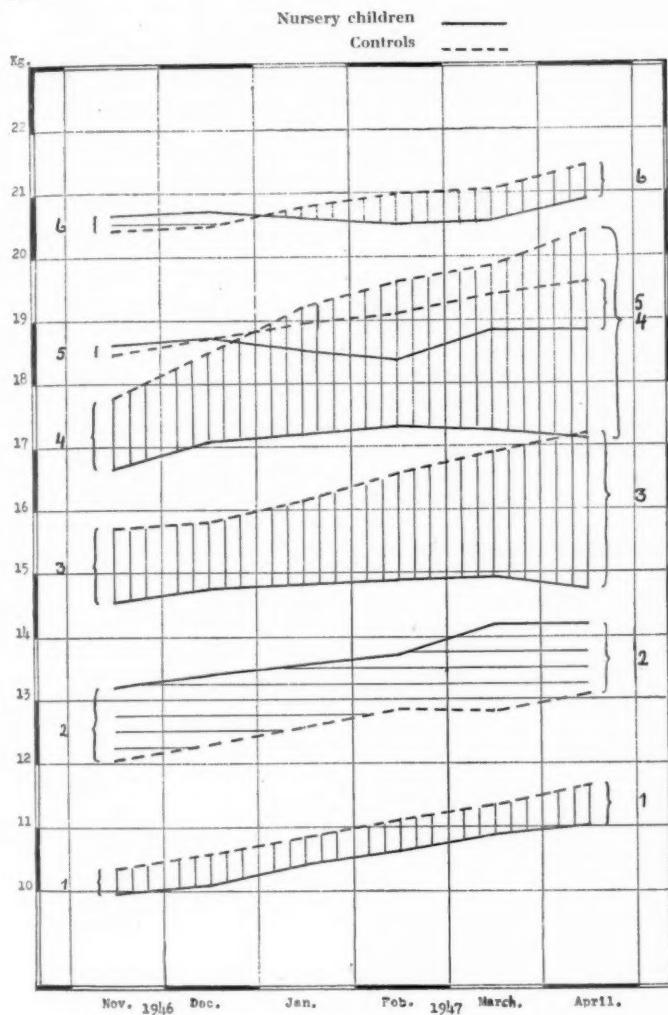


Fig. 3 b.

Fig. 1 illustrates some of the results for nursery children and corresponding controls, boys to the left and girls to the right. Groups A-D are made up of infants, children from 18 months to 3 years, children of 3-4 years, and children of 4-6 years, respectively, while the column farthest to the right gives the averages for the entire four groups. The values plotted on the ordinates correspond roughly to the number of days the given symptom was present in percentage of the examination period. The institutional groups are designated by means of hatched columns, the control groups by white ones. It is evident that the morbidity — at any rate as far as manifest in the appearance of coryza, fever and otitis — is about twice as high among the nursery children as among the home children. Concerning the different age groups in the day nursery material, the occurrence of fever has a tendency to decrease with increasing age, while coryza is most frequent in the group of 18 months-3 years, in which it attains a level of about 60 % of the examination period. The morbidity for the various age groups of the control material shows no great variations.

Fig. 2 illustrates the corresponding results for the kindergarten children. These children are somewhat older, 3-7 years, and they attended the school merely for 3 hours on the first 5 days of the week. These two circumstances are probably connected with the finding of a considerably lower morbidity among these children, even though the difference between the institutional children and the controls is considerable here too.

Naturally, the morbidity aspects among these children may be expected to have influence upon their gain in weight. How this matter stands in the present material is shown in Fig. 3. Here the children are divided into 6 age-classes, designated as 1-6. In the five younger classes both the boys and girls — except in one instance — show on an average a lesser gain in weight for the nursery children than for the controls. The oldest age group, on the other hand, showed no such difference.

It has been possible here merely to give a brief survey of some of the results obtained in these studies. Keeping in mind that these findings apply only to a single institution, covering a relatively short period, and that they cannot offhand be generalized, we still have here an illustration of the serious influence upon the state of health which collective care of children may imply, especially the youngest age-classes which ought to urge to further, primarily experimental preventive investigations.

*Erik Frisell, (Sweden).*

At the instigation of Professor Gyllenswärd, a microsedimentation test was performed in 1943 on a number of day nursery

children in Stockholm. The material comprises about 200 children, 0-7 years old, in 3 day nurseries. For control, the test was performed on a number of children in some nursing centres who in no instance had visited a day nursery. The microsedimentation rate was found to be higher for the day nursery children than for the home children, and there was a statistically established difference between the age group of 0-2.9 years and the group of 3-7 years.

These studies are published in *Acta Pædiatrica Vol. XXXV, 1948.*

*Bertil Söderling (Sweden).*

In Sweden, too, we have had some unpleasant experiences concerning laryngobronchitis fulminans toxica. In 1947 I have reported our experiences in this respect from a particularly exposed district — Borås (*Nordisk Medicin, 1947*).

It seems to me as if a controversial question has entered this subject.

Our Danish colleagues appear to look upon the disease as an affection per se that is not to be grouped together with pseudocroup. I am of a different opinion.

For one thing, I have never seen a case of laryngobronchitis fulminans toxica except among accumulations of cases of pseudocroup. (This year we have been practically free from both kinds.)

Further, we meet with numerous transitions between the two forms; and finally, undoubtedly the cases involve some widely different etiological factors.

All pediatricians know very well that some children with respiratory infections (due to streptococci, staphylococci, pneumococci, viruses or intestinal bacteria) have a constitutional tendency to pseudocroup symptoms while others never have any stenotic complications.

Perhaps also meteorological factors may play a rôle, but these cannot yet be established.

I believe that the malignant complication with a tendency to spreading downwards in the air passages, toxic affinity for the central nerve system, enormous production of fibrin, etc., is also a constitutional phenomenon and that laryngobronchitis fulminans toxica is an addition to the pseudocroup. At any rate, I think, the opposite may not be proved until we are able to demonstrate the specific infectious agent under the microscope.

*Gunnel Melin (Sweden).*

The hemophilus influenzae bacterium has occurred in our material but to very slight extent. Only a few of the younger children

have shown this bacterium in the air passages, and in very few cases may any etiological significance be attached to its presence. The Pfeiffer bacillus is not likely to play any dominant rôle as an etiological factor in upper respiratory infections among the children in Stockholm — at any rate not in the same degree as in USA where in some parts it is reported to be very common.

*From the University Institute of General Pathology.  
Head: Professor K. A. Jensen,  
and the Dronning Louise's Children's Hospital, Copenhagen.  
Head: Professor O. Andersen.*

## PERORAL ADMINISTRATION OF PENICILLIN TO INFANTS

By

K. BIERING-SØRENSEN and J. DRAGSTED (Denmark).

*Authors' abstract.*

In a series of works from more recent years it has been demonstrated that not inconsiderable amounts of penicillin may be absorbed from the gastrointestinal canal in infants.

In order to investigate the possibilities of oral employment of penicillin, in the present work we have determined the penicillin concentration in the serum in 84 infants, 6-440 days old, after peroral administration of various amounts of penicillin. Most of these children were bottle-fed. The penicillin was given in pure aqueous solution, as a rule together with the meals, as the time of its administration proved not to play any particular rôle with regard to the serum concentrations obtained.

In most of these cases the blood samples were withdrawn 1 and 3 hours after the ingestion of penicillin. The penicillin concentration in the serum was determined partly after the usual diluting method, partly after the "agar cup method".

In the graphs the penicillin concentrations are plodded along the axis of ordinates — and for the sake of easy survey we have chosen a logarithmic recording — while the number of hours after the administration of penicillin is plodded along the axis of abscissas.

From Fig. 1 it is evident that ingestion of 7000 I. U. penicillin per kg. body weight will give a satisfactory serum concentration in children under 3 months. Of children in their second quarter year of life, however, a good many show rela-

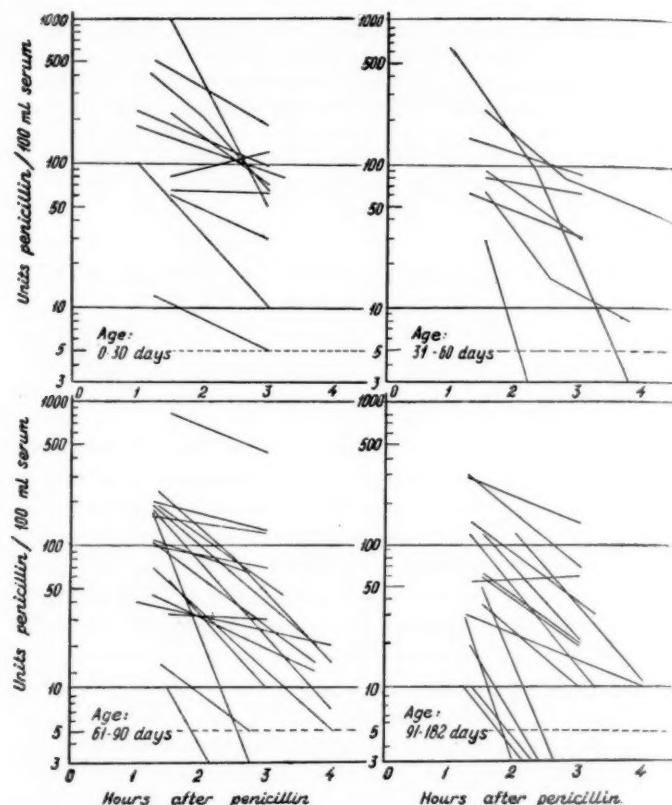


Fig. 1. Penicillin concentration in serum after peroral administration of 7000 I. U. per kg body weight.

tively low concentrations, so that for the sake of safety it is advisable to children of this age to give 12000 I. U. per kg. body weight (Fig. 2).

Good concentrations may also be obtained with 12000 I. U. in children over 6 months, but now the excretion of penicillin proceeds just as rapidly as in older children, and hence it is advisable to increase the dose, up to 25000 I. U. (Fig. 2). Con-

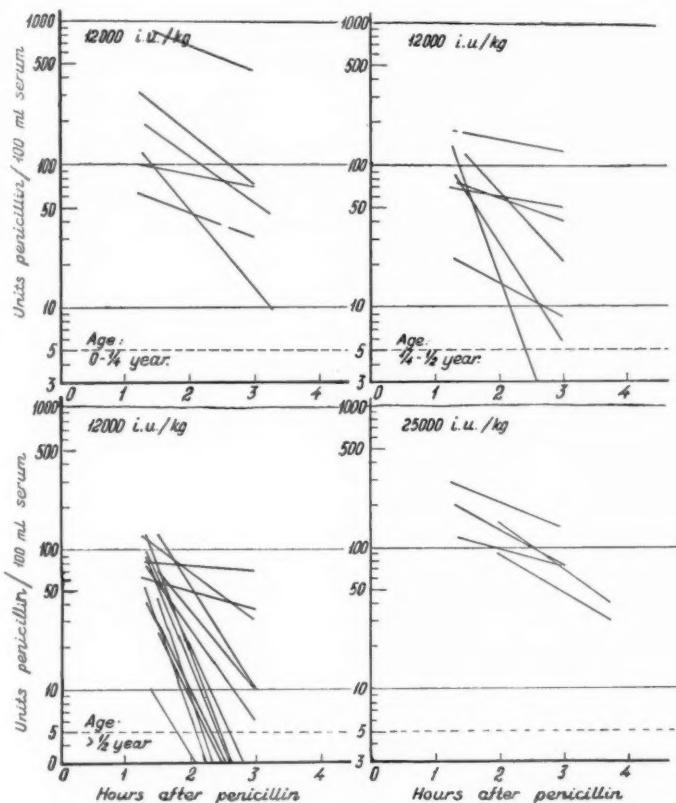


Fig. 2. Penicillin concentration in serum after peroral administration of 12,000—25,000 I. U. pr. kg body weight.

versely, in prematures we have obtained satisfactory concentrations in the first 3 months with doses as low as 3000 I. U. per kg. body weight.

With the dosage given here, with few exceptions, concentrations of over 0.5 I. U. per ml. serum were obtained, and also measurable values after 3 hours, as a rule over 0.1 I. U. per ml. serum.

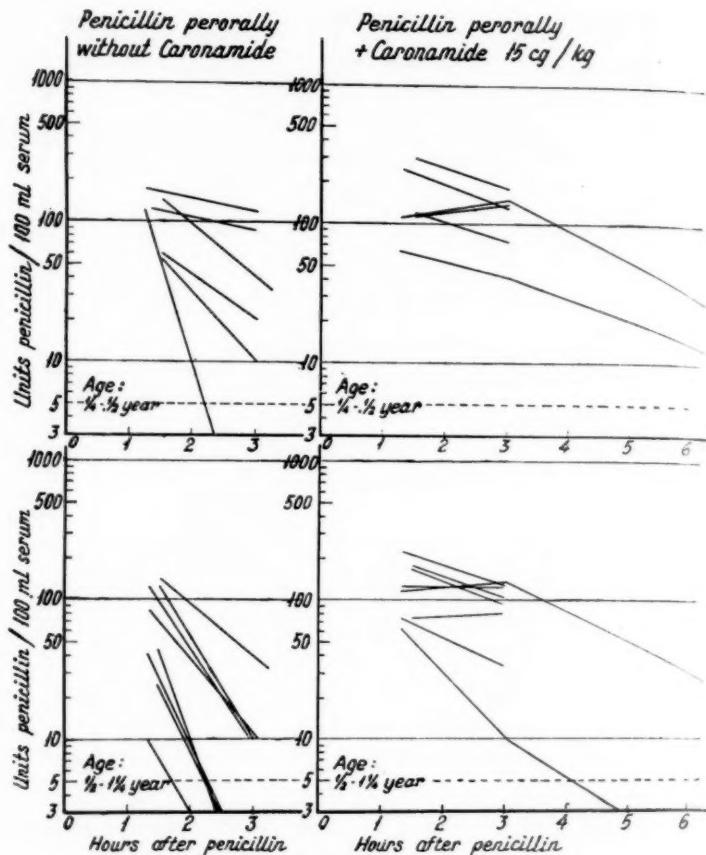


Fig. 3.

Finally, 15 children were given penicillin together with "caronamide" (4-carboxy-phenylmethanesulfonanilide), 15 cg. per kg. body weight (Fig. 3).

In this way higher and, in particular, considerably longer-lasting penicillin concentrations were obtained in the serum, especially in infants more than 6 months of age. No toxic by-effects were observed from the employment of caronamide.

*Conclusion:*

Satisfactory therapeutic penicillin concentrations in the serum may be obtained by peroral administration of 7000 I. U., 12000 I. U. and 25000 I. U. penicillin per kg. body weight to infants, respectively 0-3, 4-6 and 7-15 months old.

Simultaneous administration of caronamide gives higher and longer-lasting concentrations.

*From the Blegdam Hospital, Epidemic Department, Copenhagen.  
Head: Professor H. C. A. Lassen.*

**COMPARATIVE EFFECTS OF INTERMITTENT AND  
CONTINUOUS PENICILLIN THERAPY  
(PROCAINE PENICILLIN)**

By  
**TORBEN JERSILD**  
*Author's abstract.*

The greatest drawback in penicillin therapy as usually given at present is the repeated daily injections.

In Denmark it gradually has been realized that a few injections daily may be quite sufficient, but in most other countries the administration of penicillin every 3-4 hours is still maintained as essential.

In various places, however, attempts have been made to simplify the treatment, chiefly after the following three principles:

- 1) peroral administration,
- 2) inhibition of the excretion,
- 3) retardation of the absorption.

When given perorally, penicillin is absorbed but very irregularly. An exception to this rule appears to be found in the peroral administration to infants, in a great majority of whom penicillin is absorbed relatively well. But even within this narrow age-zone, reservation is taken when the oral treatment is given to infants with enteritis, regurgitating infants and infants on mixed diets. Further, in cases of infants suffering from severe infections the oral administration of penicillin is also unsuitable, because the clinician does not want to expose the infant to the risk of poor absorption.

An additional drawback of the peroral administration of penicillin is the fact that it is far more expensive, the doses for peroral penicillin therapy being 4-10 times higher than

the doses for parenteral administration. All told, I think, it may safely be said that the peroral penicillin therapy is still at the experimental stage.

The other principle is to delay the excretion of penicillin through the kidneys by simultaneous administration of caronamide. But caronamide is too expensive for general use.

Thus there remains the third principle: to retard the absorption of penicillin and thus reduce the number of injections required.

In December 1945, in the Blegdam Hospital, we commenced treating scarlet fever patients with only 3 penicillin-adrenaline injections in 24 hours. The penicillin-adrenaline was encumbered with certain drawbacks, however, among others, the appearance of focal necroses in some cases. We then went on to try whether we might obtain just as good results by means of 3 daily injections of penicillin without adrenaline. Indeed, this was found to give just as good results.

The next step was to see whether the number of injections perhaps might be further decreased. We therefore divided the 3 injections of 100,000 I. U. into 2 injections of 150,000 I. U., and the results obtained in this way were just as good as before. Altogether 2000 scarlet fever patients have been treated in this way.

Looking into the penicillin concentration in the blood, the effective concentration is found to keep only for 3-4 hours after the injection, and thus *it seems justified to conclude that a constant penicillin concentration is not an absolute condition for its therapeutic effect.*

It seemed obvious, therefore, to try whether also one injection daily might be sufficient. It would hardly be necessary here to point out how valuable it would be for the practising physician to be able to get along with one injection daily — and the advantages of such a procedure to the patient are equally obvious. Here, however, it turned out that the limit of simplification had been reached. (From Fig. 1 the failing effect of this form of treatment is evident.)

There now remained the possibility of trying whether the results of one injection daily might turn out better on addition

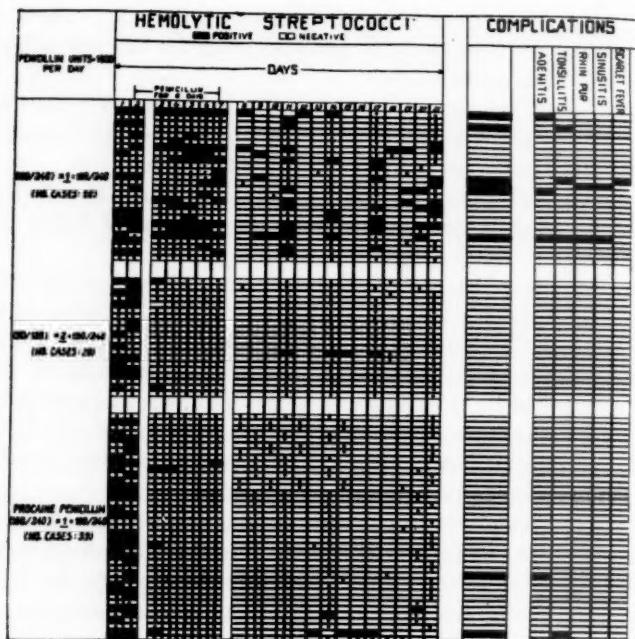


Fig. 1.

of a substance that would delay the absorption of the penicillin.

Previous investigators have shown that the absorption of penicillin may be delayed by giving it in a beeswax-peanut oil suspension, but the local discomfort associated with such injections is so pronounced that most clinicians have given up this method.

There is another way of administration, however, that appears to effectuate a protracted absorption of the penicillin without being encumbered with the drawbacks connected with the beeswax preparation, namely: employment of procaine penicillin suspended in sesame oil.

Procaine penicillin is a crystalline salt, almost insoluble in water. It is to be pointed out that procaine and penicillin enter the formation of a chemical compound, a regular penicillin

salt — in contrast to penicillin adrenalin, which is a mixture. The exact composition of procaine penicillin is: 300,000 I. U. penicillin and 125 mg. procaine suspended in 1 ml. sesame oil. This preparation is easy to inject, and it causes no local inconvenience; in contrast even to isotonic penicillin solution, it gives no pain.

The clinical and bacteriological results obtained with this preparation are evident from Fig. 1. As a measurement of the therapeutic efficacy of procaine penicillin, in the Blegdam Hospital we have studied its effect in cases of scarlet fever. The present material comprises 39 children treated with 180,000/240,000 I. U. procaine penicillin given once in 24 hours. Only in 2 patients were hemolytic streptococci found after the discontinuance of the treatment; and only 2 patients had complications (cervical adenitis in 1, tonsillitis in 1) that yielded promptly to repetition of the treatment.

For comparison, 26 children were treated with exactly the same dose of penicillin but without any addition of procaine. Fig. 1 illustrated plainly the failing effect of the latter form of treatment, as hemolytic streptococci were found in 20 of these patients after the discontinuance of the treatment, and complications arose in 6 cases.

The penicillin concentration in the blood after a single injection of procaine penicillin is evident from Fig. 2. After 9

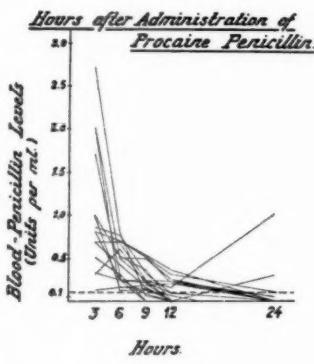


Fig. 2.

hours, 15 of the 19 patients showed a therapeutically effective penicillin concentration in the blood ( $>0.05$  I. U. per ml. serum). 12 hours after the injection of penicillin, about half of the patients still showed a concentration of  $> 0.05$  I. U. per ml. serum but after 24 hours only 6 out of 21 patients showed a satisfactory penicillin concentration in the blood.

#### *Conclusion.*

Treatment of scarlatinal patients with 1 daily injection of procaine penicillin for 6 days appears to give just as good results as 2 injections daily of ordinary penicillin (same 24-hour dose). That 2 daily injections are sufficient has been shown as early as 1946 (Jersild). One daily injection of ordinary penicillin proves insufficient (of 26 patients 20 showed the presence of hemolytic streptococci after discontinuance of the treatment, and complications arose in 6 cases).

With procaine penicillin the therapeutic penicillin concentrations in the blood may be maintained on an average for 12 hours.

Altogether 39 children have been treated with procaine penicillin, and no untoward effect whatever has been observed.

#### DISCUSSION

##### *P. Karlberg (Sweden).*

In the Norrtull Hospital, in Stockholm, in the past year we have commenced treating infections of the air passages in infants by means of aerosol inhalation of penicillin. For this purpose we have constructed a simple plastic hood to place over the head of the child. The construction of the hood is evident from Fig. 1. The penicillin is introduced from behind through a tube in the top of the hood. Different spraying apparatuses have been tried, and the American oxygen-driven Barach atomizer. It is small, easy to manage, relatively inexpensive — and at the same time it affords an extra addition of oxygen that often is desirable in infections of the air passages.

The child is treated for 10 min., 4-6 times daily, with doses of 20,000-60,000 I. U. penicillin. In order to check up the absorption of penicillin and, in particular, for comparison with injection



Fig. 1.

therapy, on 15 children we have made serial determinations of the penicillin concentration in the blood serum, 30, 60, 120 and 180 min. after inhalation of penicillin as well as after intramuscular injection of ordinary penicillin in usual doses. (The determinations of the concentration were performed in the State Bacteriological Laboratory by Dr. G. Wallmark.)

The inhalation was found to give about the same concentration apex after 30 min. as was found for intramuscular injections, and the excretion of the penicillin did not proceed more rapidly. In no case did the serum penicillin concentration fall below the level of 0.06 I. U. per ml. serum given in the literature.

As penicillin is absorbed through the tissues of the air passages, the penicillin concentration will undoubtedly be higher in these tissues on inhalation of penicillin than on injection, when penicillin reaches these tissues from the blood stream.

A number of cases of various infections of the air passages have been treated after the inhalation method, with good results — partly as the only form of treatment, partly supplemented with administration of penicillin in some other way.

Thus inhalation treatment with penicillin is available also to infants, and it has to be looked upon as a valuable adjuvant in the treatment of infections of the respiratory passages — especially in infants, in whom such infections often are apt to take a serious course. Whether this form of treatment is to be completed with some other administration of penicillin has to be judged from case

to case. For supplementary treatment, in particular for the smallest infants, administration of penicillin by mouth appears preferable, with avoidance of injection.

*T. Salmi (Finland).*

In the Pediatric Clinic of the Åbo University, Finland, we have carried out some studies on the penicillin titer of serum in prematures who were given penicillin by mouth, dissolved in saline, that is, without addition of a buffer solution. Generally the dose has been 4000-5000 units, i. e., about 2000 units per kg. body weight. The penicillin titer in the blood was determined after Rammelkampf's method.

The purpose of these studies was to establish when the penicillin dose ought to be given in relation to the meals in order to obtain the highest penicillin titer possible and how the simultaneously observed pH values for the stomach contents might influence this titer.

The studies are still far from being concluded, but it still seems justified from the results obtained to draw the following conclusions.

1. Peroral administration of penicillin without buffer solution to prematures gives the penicillin titer in the serum corresponding to therapeutic values. The penicillin titer in blood samples withdrawn 1 hour after administration of the penicillin generally amounts 3-4 times the therapeutic value, and within 3 hours it falls to the therapeutic minimum, 0.03 unit per cc. serum.

2. It appears as if the highest penicillin titer may be obtained by giving the penicillin during the latter half of the interval between two meals.

3. This seems to be the case in spite of the fact that the stomach contents are found to increase in acidity with increasing interval after the preceding meal of mother's milk, the acidity values varying from pH 6 to about pH 2.

*From the Radium-Centre.*

*Head: Jens Nielsen,*

*and the Danish Cancer-Regist "n, Copenhagen.*

*Head: Johs. Clemmesen, M. D.*

## CANCER IN CHILDHOOD

By

AAGE VIDEBAEK (Denmark).

*Author's abstract.*

The necessity is stressed of being "cancer minded" also at the sick-bed of a child. It is true that the incidence of cancer in childhood cannot be compared with that of older age groups, there being in Denmark in the age group of 0-10 years about 2 cases of cancer per 10,000 living children, whereas the corresponding figure, for instance, in the age group of 70-74 years is about 130, but the chances of cure in childhood are so minimal that cancer occupies an important position in the statistics of causes of death. During the period of 1937-46, in Denmark, 415 children died of pulmonary tuberculosis, 429 of heart disease, 502 of measles, but not less than 544 of malignant tumors. Among malignant tumors occurring in childhood, systemic diseases predominate (30 %), especially leukemia, but also Hodgkin's disease, lymphosarcoma, reticulum cell sarcoma, and myelomatosis play a part. Second in frequency is sarcoma (about 20 %), particularly osteogenic sarcoma. Intracranial tumors make up about 20 %, skin carcinomas about 4 %, renal tumors (especially Wilms') about 4 %, while tumors of the alimentary tract constitute about 3 % and cancer of the genital organs about 2 % of all cases of cancer in childhood. Accordingly, malignant growths in childhood occupy an exceptional position, both as regards localization and histological aspects, although almost any organ may be involved in childhood too. In the age group of 0-14 years about 80 % of all malignant growths are sarcomas, but after the 50th year of age the percentage of sarcoma is below 10.

## DISCUSSION

*Matti Sulamaa (Finland).*

A statistical account from the Children's Hospital in Helsinki concerning the frequency of malignant tumors shows that among nearly 10000 patients admitted 23 were suffering from unquestionable malignant tumors and 6 from probable malignant tumors.

Sarcomas, above all, Wilms' tumor, constitute the largest group.

On comparison with tumors in adults, the possibility of successful treatment and the prognosis are worse for the children. The prognosis is aggravated chiefly through the circumstance that an early diagnosis is not made so often in these patients, and that palliative treatment is not so desirable here as in adult patients. Further, the relatively slight tolerance of the little patients naturally reduces the serviceability of extensive radical operations. Thorough collaboration with the radiologists seems highly desirable.

Table 1.  
*Survey of Tumor in the Children's Hospital in Helsingfors  
1/1 1946 to 1/8 1948.  
Total of first admissions: 9500.*

*Malignant tumors: 23 + 6?*

	No.	Age	Duration of ill- ness before adm.	Remarks
Adenosarcoma of the kidney (Wilms' tumor) .....	9	7 mths.	4 days	Died 2 months aft. op.
	10	»	2 months	Died in hosp.
	11	»	2 »	
	13	»	6 »	
	14	»		myxedema
	16	»	1 month	
		2 years	3 weeks	
		2 <sup>1</sup> / <sub>12</sub> »	1 <sup>1</sup> / <sub>2</sub> months	
		5 <sup>7</sup> / <sub>12</sub> »	1 month	Died 4 <sup>1</sup> / <sub>2</sub> months aft. op.
Lymphosarcoma .....	4			
mediastinal .....		2 months	3 weeks	Died in hosp.
retroperitoneal .....		3 <sup>1</sup> / <sub>2</sub> years	2 months	Died in hosp.
cervical .....	10	»	4 »	
orbital .....	13	»	3 »	

	No.	Age	Duration of illness before adm.	Remarks
Sarcoma, reticulocellular . . .	1	1½ months	Since birth	Died in hosp.
Sarcoma, spindle-cell . . . . .	1	2 months	1 month	Died in hosp.
Melanosarcoma of eye . . . . .	1	4 years	2 months	Died in hosp.
Fibrosarcoma of anal region	1	2 months	Since birth	
Osteosarcoma . . . . .	4			
of pelvis . . . . .		9 years		
» » . . . . .	13	»	2 months	
» tibia . . . . .	9	»	1½ »	
» femur . . . . .	4	»		Died in hosp.
Seminoma . . . . .	1	2½ years	1 year	Died in hosp.
Carcinoma, medullary, of the colon . . . . .	1	9 years	2 months	

*Benign tumors: 92*

Benign abdominal tumors . . . . .	7			
Enormous cyst of gastrocolic lig. 1		Tumor of the brain . . . . .	10	
Duplication of the colon .. 1		Teratoma . . . . .	9	
Cyst of the kidney . . . . 3		Dermoid cyst . . . . .	8	
Adenoma of the kidney .. 1		Hemangioma . . . . .	37	
		Other benign tumors . . . . .	21	

*Undetermined abdominal tumors: 6 (including 3 probable adenocarcinomas of the kidney).*

*From the Surgical Department at the Children's Hospital,  
Helsingfors.*

*Head: Matti Sulamaa, M. D.*

## **ON THE MORTALITY IN INFANTILE SURGERY AND ITS CAUSES**

*By*

**MATTI SULAMAA (Finland).**

*Author's abstract.*

The mortality in the Surgical Department of the Children's Hospital, Helsingfors, in 1947 was 9.5 %. For the age of up to 3 months it was 30 %, for 3-12 months it was 15 %, for 1-3 years, 4 %, and for 3-15 years, 1.5 %. In all these age groups the severity of the original illness was practically the cause of death in half of the cases. In the other cases some diagnostic or therapeutic error was ascertained. Among the children under 1 year, nosocomial septic enteritis was the cause of death in 10 % of the fatal cases. Measures for the avoidance of secondary infections and fatal errors are discussed.

(Published together with N. Schwanck in Nord. Med. 1949.)

*From the Pediatric Clinic at Norrtull's Sjukhus, Stockholm.  
Head: Professor A. Wallgren.*

## A SIMPLIFIED QUANTITATIVE METHOD FOR THE EXAMINATION OF URINE SEDIMENT

By

STIG NORSTEDT and LENNART SILVERSTOLPE (Sweden).

*Authors' abstract.*

The method\*) is founded on the specially constructed centrifuge tube\*\*) shown in Fig. 1. It is constructed so that on removal of the bottom stopper (while holding the tube vertically) this stopper will carry in its cavity a constant quantity of the liquid (= the sediment), while the rest of the liquid remains in the tube.

In order to get a quantitative centrifugation we have tried to eliminate the currents rising in the centrifuge tube during the centrifugation, especially at the slackening of the speed, by a cardanic suspension\*\*\*) of the casings of the centrifuge tubes.

We have also looked into what might be the most suitable centrifugal effect for blood corpuscles in urine. *The best effect is obtained at 2000 r. p. m. for 3 minutes.*

One important source of errors is the fact that when nephritic urine is left standing at room temperature the red blood cells are destroyed rather quickly. This is evident from Fig. 2, which shows 300 urines separated in 3 different groups according to their specific gravity. It is surprising that the higher the specific gravity of the urine, the more quickly will the red blood corpuscles be destroyed. *This shows the importance of the urine being examined as soon as possible.*

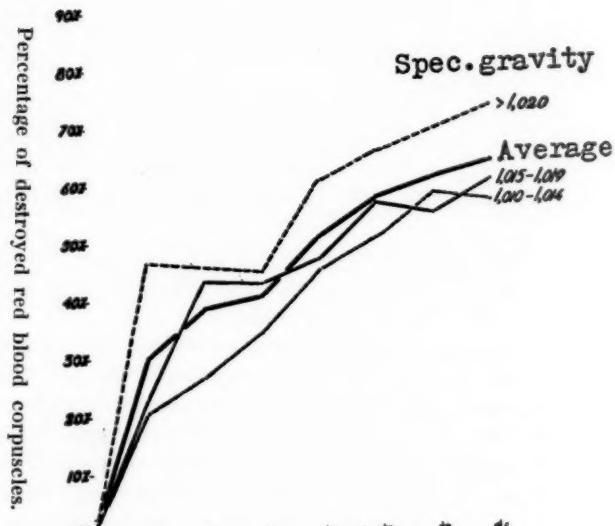
\*) preliminarily demonstrated by Silverstolpe and Müller (Lausanne) 1947.

\*\*) demonstrated by Silverstolpe 1946, fabricated by Rudolph Grave, Stockholm, Sweden.

\*\*\*) This type of centrifuge is made by KIFA, Stockholm, Sweden.



Fig. 1.



Time in hours the urine has been standing at + 19° C.

Fig. 2. The rapidity of red cells being destroyed in nephritic urine from children.



Fig. 3. 24-hours curve.

Excretion of red corpuscles. Average value for 13 nephritic cases (children of 3-12 years).

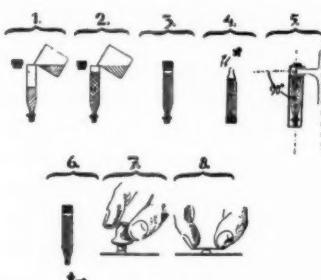


Fig. 4.

1. 5 ml. fresh morning urine.
2. 0.9% NaCl to the 10 ml mark.
3. Top stopper in. Mix well.
4. Let out the over pressure.
5. Centrifuge at 2000 r.p.m. for 3 minutes.
6. Screw out the bottom stopper with the sediment.
7. Put out the sediment on the slide.
8. Let a cover-slip of constant size and weight (e.g.  $18 \times 18$  mm.) fall on the sediment.

Count 10 sights fields (red cells, white cells, epithelial cells) in the microscope in two perpendicular directions (magnif.  $\times 400$ ). Count the casts in 10 fields (magnif.  $\times 90$ ). Answer in one field; correction made for the dilution. Normal values: 0-1 red cells, 0-6 white cells, 0-1 hyaline cast per field.

Another matter of importance is the hour of collecting the sample. Both curves in Fig. 3 represent the average value of the excretion of red blood corpuscles from 13 children with nephritis. In this way you may observe a regular rhythm of day and night of the excretion of red blood corpuscles in the urine of nephritics, and the value may vary up to 300 % in the same 24 hours (the patients being kept in bed all the time). *This physiological variation points at the necessity of collecting the samples at the same hour* in order to get comparable values from one day to another. When the children have let the night urine about 6 o'clock give them something to drink and collect the fresh morning urine about 8 o'clock for examination. Fig. 4 shows how the method then is performed.

We cannot find any reason for preferring the method proposed by Addis, which is difficult to perform and takes a lot of time. Therefore, at the Norrtull hospital in Stockholm, we have now changed to this new, simple quantitative method for examination of urinary sediment in children.

*From the Hospital for Allergic Diseases, Drumsö.  
Head: Zaida Eriksson-Lihr, M. D.*

## HOW TO ORGANIZE THE TREATMENT OF ALLERGIC DISEASES IN CHILDREN

By  
**ZAIIDA ERIKSSON-LIHR (Finland).**

*Author's abstract.*

The interest in allergic diseases has greatly increased since it has been recognized, that these diseases prevail in all social classes and among people of all ages.

Now one reckons that about 7-10 per cent of the population suffers from allergic diseases to such an extent, that they are compelled to seek medical care, whereas 45-50 per cent at some time of their live have had an attack of such a disease. In adults 50 per cent of the asthma cases have begun in childhood, in children more than 75 % of the cases develop their asthma before the age of 5 years. Fig. 1.

Asthma and other allergic diseases in children show a good curative tendency when properly treated, whereas untreated or wrongly treated there is a great tendency to invalidity, especially in adults. See Fig. 2.

Thus it should be a compelling duty of the pediatrician to give these diseases the necessary attention. This fact has already for a long time been recognized in the Anglo-Saxon countries, especially in U. S. A., where in most of the larger children's hospitals there is an allergy clinic. Also in most Scandinavian countries such clinics have lately been established.

The treatment of allergic diseases is not merely a medical question, it is a question of great social-medical importance, because of the tendency of these diseases to involve whole families for generations and cover a patient's whole lifetime

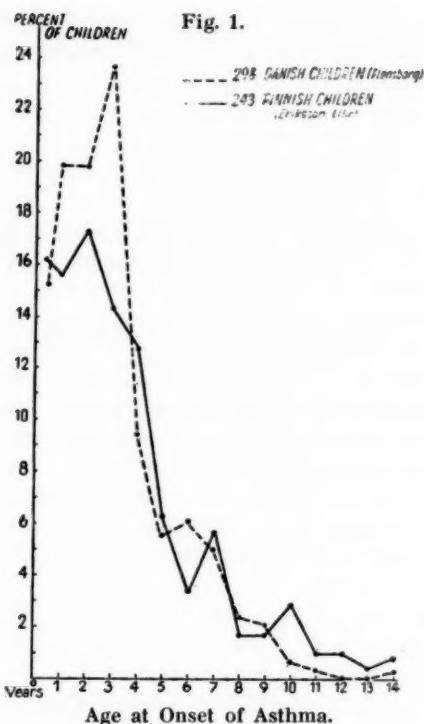


Fig. 1.

and perhaps lead him on to invalidity, needing the care by the state or the community.

In the solving of this problem the pediatrician should stand in the foreground, in close cooperation with other specialists, such as internists, dermatologists, roentgenologists, otolaryngologists and others.

This collaboration would be greatly improved by the founding of *Central Hospitals for Allergic Diseases*, with all the specialists mentioned above working under the same direction under the same roof, as seen in Fig. 3.

A hospital of this kind

- 1) gives the patient adequate, competent and centralized treatment,

Fig. 2.

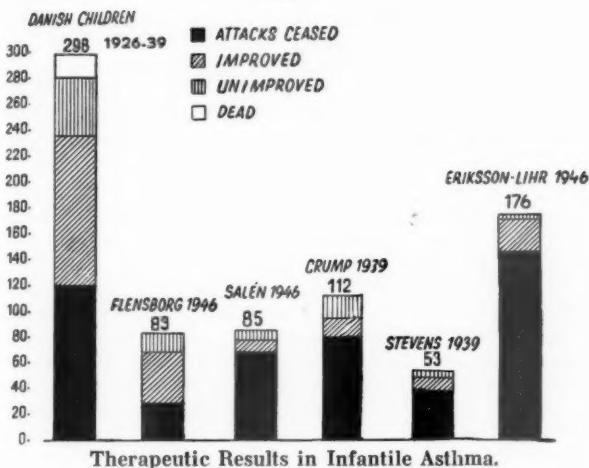
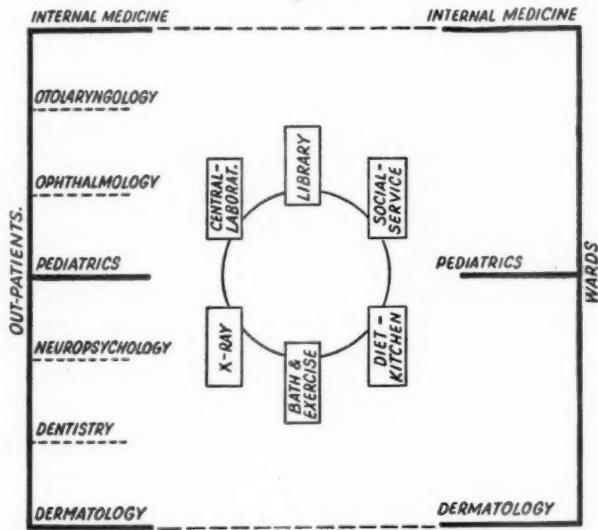


Fig. 3.



- 2) offers the physicians the facility of a thorough collaboration and possibility of research work and specialization in various fields of allergy,
- 3) and enables medical students as well as more experienced physicians and other hospital personnel to obtain instructions in the care for the allergic patient.

## DISCUSSION

### *Sven Kraepelien (Sweden).*

At the Norrtull Hospital in Stockholm, an allergic out-patient clinic for children was established 1½ years ago. Judging from the number of patients applying for medical advice, this clinic has been greatly needed. The clientele is made up chiefly of asthmatic children from the city of Stockholm, but also a considerable number of patients from all parts of the country come to this clinic.

The polyclinical work consists primarily in separating from the heterogeneous mass of admissions those patients in whom the occurrence of an allergic condition may reasonably be suspected. With regard to the relatively small number of beds in the hospital available for the care of these allergic children, a great deal of the time-consuming analytical work has to be carried out polyclinically, so that the hospital beds are occupied only by patients requiring treatment that cannot be given ambulatorily.

The polyclinical work consists primarily in the taking of an accurate and detailed history of the patient. With regard to the significance of focal infections in these asthmatic cases, besides roentgenography of the lungs, x-ray plates are also taken of the sinuses and adenoids on all the patients — sometimes roentgenography of the teeth, too. After this, the otologist is consulted and any required sanation of the focus is carried out when such a measure is indicated. In keeping with the data in the history of the patients, then, a skin test is performed intracutaneously — as a rule with about 40 standard antigens of nutritive as well as inhalatory types. To a large extent, furthermore, extract is made of dust from the patient's home. Often it may be very difficult to trace the active allergen in the given cases, and not infrequently the studies in the clinic have to be supplemented by visits to the patients' homes by the physician himself or by the curator of the hospital.

According to the data of the history of the patient and the outcome of the tests supplemented with experiments with exposure

and passive homologous transmission, the desensitization is performed after the patient has been hospitalized. This so-called quick desensitization is continued with monthly injections through the following year or two in the out-patient clinic or given by the physician in the patient's home town, who receives the extract mixtures from the clinic. The collaboration with these colleagues working in the periphery proceeds very satisfactorily, without any friction.

In those cases where specific desensitizing treatment is out of the question, the general hygienic measures are sometimes supplemented with unspecific desensitization. Also vaccination with polyclonal antidiarrheal vaccine is sometimes employed. In refractory cases experiments are made with visits to mountain resorts.

Most of these children present neurolabile stigmata, and in many cases mental factors appear as contributory to the eliciting of the asthmatic trouble. There is an intimate cooperation with the psychiatrists attached to the hospital.

As is evident from the principles here outlined, the greater part of the work is carried out in the out-patient clinic and only those cases which are more difficult to decide on and those requiring some specific therapy are hospitalized.

Unfortunately, our observation period is still too short for any estimate of our therapeutic results. But so far our results have appeared to be favorable, on which account we shall continue on the road we have taken.

#### A. Lichtenstein (Sweden).

It is regrettable that time does not permit a thorough discussion of the interesting paper given by Dr. Eriksson-Lihr. Much may be said pro but also much contra the project presented in that paper. I will have to limit myself to say as my personal opinion that I do not believe it would be a fortunate thing to establish all too many different kinds of special hospitals for children, and that it would be better to have special departments — also for allergic diseases — within the scope of the pediatric clinic.

STUDIES ON CHANGES IN THE SYMPATHETIC GANGLIA  
OF THE PYLORIC PORTION OF THE STOMACH IN  
INFANTS WITH PYLOROSPASMS

By

HILMA ALAROTU (Helsinki, Finland) and ERNA CHRISTENSEN  
(Copenhagen, Denmark).

*Authors' abstract.*

At the initiative of Docent Räihä, on material from the Children's Hospital in Helsinki, histological studies have been carried out on the pyloric portion of the stomach from 29 infants who died under the clinical diagnosis of pylorospasm, in order to ascertain whether any changes might be demonstrated in the sympathetic ganglia in this region.

For the sake of control corresponding studies were carried out on this part of the stomach from 26 infants who had been suffering from gastroenteritis and 21 infants who had died of other diseases, without any clinical symptoms of any gastrointestinal infection.

The 29 infants with pyloric stenosis were from 14 days to 6 months old, 13 of them being one month or less, and only 2 of them over 3 months old. In most of these cases the disease had lasted or, rather, had been manifest for about 1 month.

The material further includes a biopsy on a child 1½ months old, admitted to the pediatric dep. of the Rigshospital, Copenhagen, with pylorospasm and treated operatively. In this case, too, the disease had lasted one month.

In most of these cases a solution of formalin or acetic acid alcohol was injected into the stomach from 2-6 hours after death for prevention of post-mortem changes. The specimens were embedded in paraffin, and the sections were stained with hematoxylin-eosin and also after v. Gieson's, Einarson's and Bodian's staining methods.

All the pylorospasm specimens showed disorganization in the structure of the ganglia with glia proliferation, varying in intensity, and degeneration of the nerve cells with shrinkage of the protoplasm as well as of the nuclei.

The specimens from cases of gastroenteritis showed round-cell-infiltration, edema of the ganglia and, in some cases, degeneration of the nerve cells together with glia proliferation, the latter of which apparently was dependent upon the duration and intensity of the disease.

The remaining 21 control specimens showed practically no changes other than what might be ascribed to post-mortem influence upon the nerve cells.

From these studies it cannot be decided whether the changes demonstrated in the ganglia are primary or secondary, but they open fairly wide perspectives concerning the pathogenesis and treatment of pylorospasms.

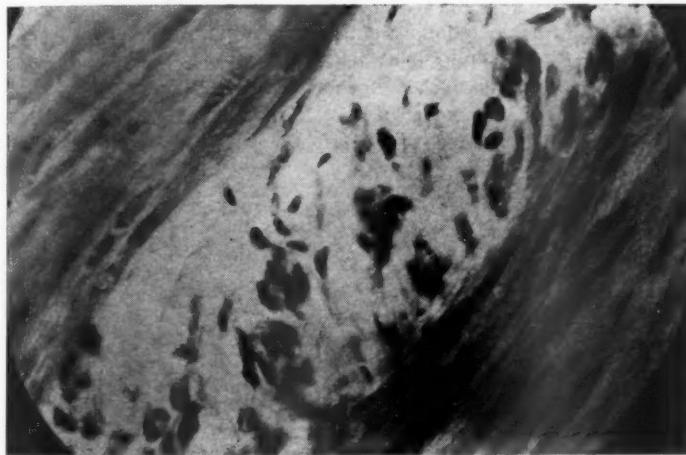


Fig. 1. Biopsy specimen from a 6-week-old patient with pylorospasms (duration of illness: 1 month).

Sympathetic ganglion showing disorganization, nerve-cell degeneration and glia proliferation.

Magnif.  $\times 300$ . Einarson staining.

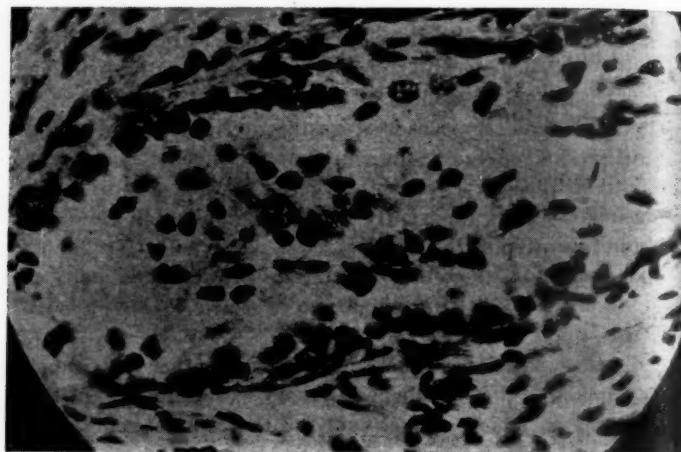


Fig. 2. Specimen from a gastroenteritis patient, 7 weeks old, in whom the disease had lasted 3 weeks.

Swelling of the ganglion, slight degeneration of the nerve cells and slight glia proliferation.

Magnif.  $\times 300$ . Einarson staining.

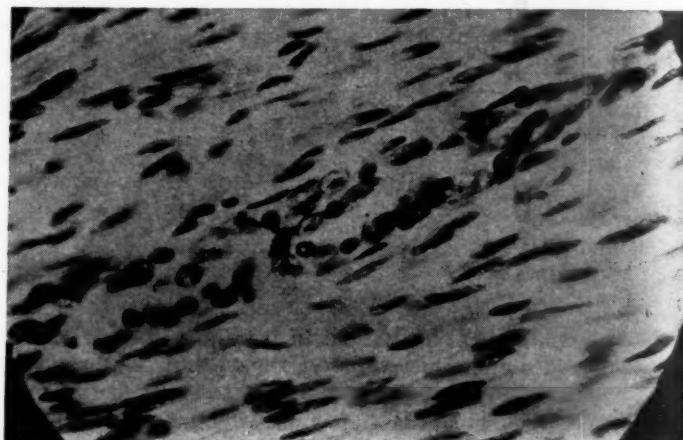


Fig. 3. Specimen from a premature child, 1 month old, with icterus neonatorum; ill since birth.

Normal sympathetic ganglion.

Magnif.  $\times 300$ . Einarson staining.

## DISCUSSION

*C. E. Räihä (Finland).*

In 1937 Ylppö and I published a paper on pylorospasm in which we stated that many things suggest that this morbid condition arises as a result of irritation of the mucous membrane of the stomach, especially the pyloric portion, and that the seasonal distribution of the patients showed accumulation of cases in the spring and late summer, that is, at times when we meet with an increase in the frequency of infectious diseases. In this paper we also reported the case of an infant who was operated in which the surgeon considered the diagnosis erroneous, as no hypertrophy of the pyloric musculature could be demonstrated. Subsequently this case developed further and took the usual course of pylorospasm.

In 1946 Wallgren pointed out that pylorospasm is not encountered immediately after birth and that later, at the age of 3 weeks, the theoretically expected number of cases develop. Wernstedt takes pylorospasm to be a disturbance of the coordination in the motor mechanism of the stomach.

At the last congress in Helsingfors I reported that together with Alarotu we had found changes in the intramural nervous system of these patients, and now Christensen and Alarotu have analyzed this finding with the result that has been reported here. We find regular inflammatory signs in the mucous membrane as well as in the perivascular connective tissue, and evidence of degeneration in the nervous system.

On summing up briefly what we know about the physiological function of the pyloric muscle, it will be as follows: the muscle is in a state of tonic contraction, so that the pylorus is closed continuously, except when it opens for evacuation of the fluid stomach contents. This opening of the pylorus is regulated through intramural reflexes, elicited partly from the stomach, partly from the duodenum. The vagus further transmits the reflexes that make the pylorus open, while the sympathetic nerve system inhibits them. By administration of ergotamine and electric stimulation of the vagus it has been possible to make the pylorus stand open as a tube; and by division of the vagus a continuous closing of the pylorus has been produced. All remedies with a paralyzing effect on the vagus — above all, atropine — may therefore tend to inhibit evacuation of the stomach and prevent vomiting in the same degree as they inhibit the gastric peristalsis. In pylorospasm associated with duodenal ulcer atropine is considered contraindicated, and ergotamine is often serviceable. Indeed the latter remedy has been recommended in infan-

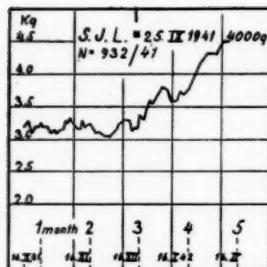


Fig. 1.

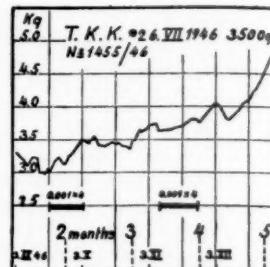


Fig. 2.

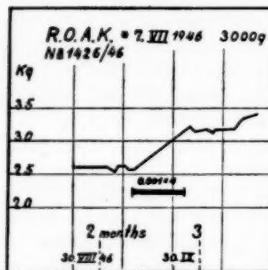


Fig. 3.

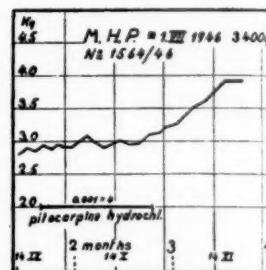


Fig. 4.

tile pylorospasm. We have also tried this remedy without being convinced about any positive result. On the other hand, toxic by-effects are claimed to be not infrequent though we never have had any disagreeable experiences in this respect.

In order to ascertain what effect might result from stimulation of the vagotonic condition, we have been treating our cases of pylorospasm with pilocarpine for 3 years. The results are not brilliant. It appears as if the contracted musculature were refractory even to this remedy, while the increased gastric peristalsis improved the evacuation, and in such cases we often obtained a gain in weight. Heikel has followed these cases roentgenologically and published his findings; he is convinced that after pilocarpine we often obtain an increased evacuation of the stomach into the intestinal canal. It will be appropriate, I think, to show two weight curves which are typical for our cases of pylorospasm, one before the pilocarpine therapy and one during the treatment with pilocarpine.

I wish to emphasize particularly that the patients admitted to

our clinic have been very ill. I have arrived at the view that often it is the primary or secondary severe infectious disease that is able to prevent a gain in weight even though we were able to give these patients sufficient food and also to get a part of this food to pass through the pylorus. During convalescence after a severe infection in very young children, we often meet with blocking of the assimilation.

*A. Wallgren (Sweden).*

Is it histologically practicable to distinguish between ganglion cells that originally were normal and subsequently became degenerated and cells that look degenerated because they are inferior from the start. Indeed, it seems conceivable that it may be a secondary phenomenon in pyloric stenosis, the degeneration being produced by the muscular hypertrophy which, hypothetically, may be taken to choke the blood supply to the location of the ganglion cells and in this way give rise to degeneration of these cells. To me it seems difficult to imagine that some preceding infection or other injurious factor might have given rise to the nerve cell degeneration at the age of about a week, prior to the development of the muscular hypertrophy. Indeed we have reason to think that children as a rule are born without any change in the pylorus and that they acquire them at an age of 3 weeks — according to the roentgenological studies we have carried out. Not long ago — in the congratulatory book to Rohmer — I read about a case in which laparotomy had been performed on the erroneous diagnosis of pyloric stenosis. Two weeks later the child was operated on again — this time with the positive finding of pylorostenotic muscular hypertrophy.

*C. E. Räihä (Finland).*

In collaboration with Ylppö we have published a case similar to the one now mentioned by Prof. Wallgren.

From the investigations reported by Kostojanski we know that an organ does not react to acetylcholine before the vagus synapse with the periphery has been established. This affords a possibility of investigating the significance of the vagus to the appearance of the clinical picture here involved.

## CONGRESSIONAL EXHIBITION

This exhibition, of scientific character, was arranged by Dr. E. Winge Flensburg.

The following subjects were dealt with:

*From the Pediatric Department, University Clinic at Rigshospitalet,  
Copenhagen.*

*Head: Professor P. Plum.*

## STUDIES ON THE DUODENAL JUICE

By

HENNING ANDERSEN and CLAUS DUEHOLM (Denmark).

The exhibition shows withdrawal and examination of the duodenal juice in children, together with a preliminary account of the enzymic values obtained in normal children and in children suffering from various affections of the digestive tract.

*Withdrawal of the duodenal juice is performed by means of a special double-tube. The stomach is drained permanently through one of these tubes while the other tube, which is somewhat longer, collects the duodenal juice. This principle of withdrawal has not been employed previously in children.*

*The double-tube is of such a calibre (outer diameter of each of the tubes: 2 mm.) that it can pass through the nose. Prior to its use, the tube is greased with exploration cream, and, after anesthesia of the nasal mucosa with 2 % pantocain solution, it is introduced down into the stomach, 30-60 cm. from the nostrils. It is important not to push the tube too far down, as otherwise it will curl up instead of passing through the pylorus. By means of a thin string and a piece of adhesive tape, the tube is fastened to the ridge of the nose. The arms of the child are fastened by means of cuffs.*

It is preferable to introduce the tube in the evening and leave it alone until next morning. In about two thirds of the cases the longer tube will then be situated in the duodenum. In dubious cases, X-ray examination is performed for the sake of control. If the tube is not in its proper place, a new attempt will have to be made later on.

The child should be fasting for about 5 hours prior to the withdrawal, which is performed by means of two Record syringes continuously for 15-30 min.

*The duodenal juice* will normally be constantly basic, clear, homogeneous throughout the experiment, whereas the yellow colour may vary with the addition of bile.

*The enzymic determinations* have been performed chiefly on the basis of Henrik Lagerlöf's "Pancreatic Function and Pancreatic Disease", Stockholm 1942. The trypsin, amylase and lipase activities are determined. In addition, pH and the icterus index are measured.

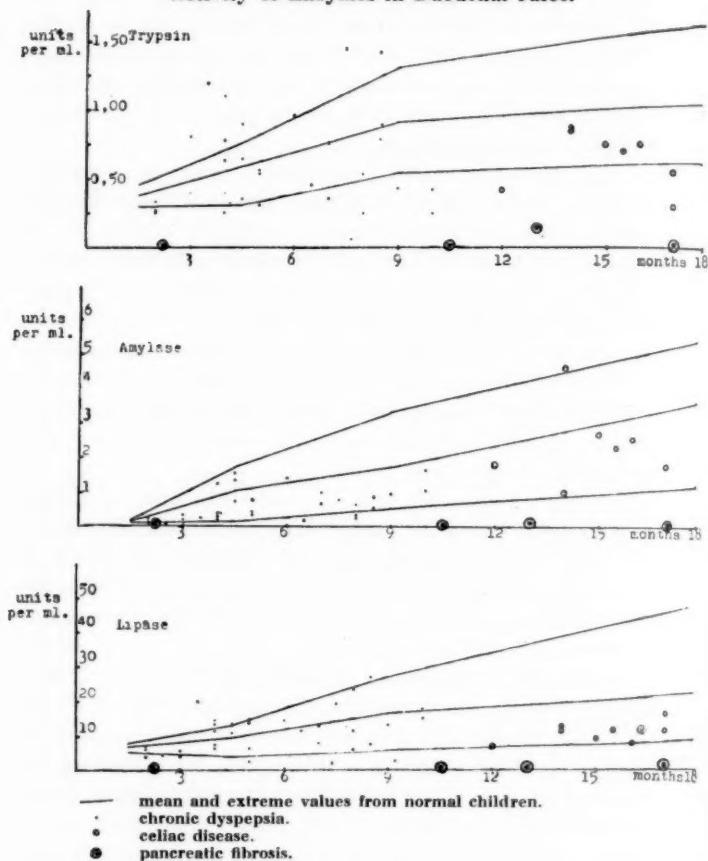
The trypsin analyses are based on the Willstätter principle as modified by the Carlsberg Laboratory: 6 % casein Hammarsten is split by the trypsin, and the carboxyl groups thus liberated are determined titrimetrically with a 0.1 n alcoholic KOH solution. As elaborated by us the method allows of determinations on amounts of juice as small as 0.5 ml., among other reasons, by titration in penicillin flasks, so that the atmospheric CO<sub>2</sub> is excluded. The amount of KOH employed for the titration, which is a measurement of the trypsin content, is converted by means of a curve plotted experimentally for trypsin units per ml. duodenal juice, corresponding to the units adopted by Lagerlöf.

*Amylase:* Nørby's method as modified by Lagerlöf. The amylase splits the starch to maltose. Within certain limits the amount of enzyme employed for this is expressed by the amount of maltose obtained, which is determined by titration.

Owing to the slight amount of amylase in children under 3 months it is essential in such cases to employ dilutions 1 : 10 — 1 : 40 instead of the usual dilutions 1: 200—1 : 800.

*Lipase:* The Rona-Michaëlis method is employed: the pancreatic lipase splits a saturated tributyrin solution, and the

## Activity of Enzymes in Duodenal Juice.



resulting increase in the surface tension is measured stalagmometrically with a Traube-Lebedens stalagmometer.

In the system adopted by us the counting of the drops is performed by means of a mercury-spring switch which is hit directly by the falling drops, closing a circuit with a writer, which by means of a special switch is able also to mark the point of time when the surface of the fluid in the stalagmo-

meter passes the upper and lower marks on the apparatus. In this way the drop count can be performed with an accuracy of about 0.1 drop.

*The gelatin film method* (H. Schwachmann) is a quick and simple method for the demonstration of trypsin. A piece of an ordinary dark X-ray film is scraped free from the gelatin membrane on one side. A drop of diluted duodenal juice is placed on the other side of the film which then is incubated at 30° in a moist chamber. After 30 min. the drop is washed off with cold water. If there has been any trypsin in the specimen of duodenal juice, the gelatin membrane will be dissolved at the site of the drop, appearing now as a clear spot. The incubation may be performed at 37°, in this case one is working near the temperature of fusion for the gelatine; it is therefore necessary, simultaneously to check with a drop of water.

Normal duodenal juice will prove active in dilutions 1 : 20—1 : 40, whereas in cases of fibrosis of the pancreas the duodenal juice will prove inactive or but slightly active even in undiluted state. Juice withdrawn with an ordinary duodenal tube is serviceable on employment of this method.

*The results* are recorded in the following tables and graphs. Summarizing the preliminary findings, the following features may be established:

1. The enzyme concentrations increase with increasing age of the subjects.
2. At the age under 3 months the amylase values are very low.
3. In cases of pancreatic fibrosis the duodenal juice shows only an exceedingly slight enzymic activity or none at all.
4. In chronic dyspepsia the amylase values appear to be low.
5. In celiac disease the activity of all the enzymes in the duodenal juice appears to be rather low. Still, in these cases as well as in the preceding (4), the values obtained show a rather wide dispersion.

**Table 1.**  
**Normal Values.**  
**Enzymic Units per ml. of Duodenal Juice.**

Age	Number	Trypsin		Amylase		Lipase	
		mean	mean	mean	mean	mean	mean
0— 3 mths. ....	2	0,39	0,47	0,14	0,17	6,8	7,8
			0,30		0,10		5,7
3— 6    >    ....	6	0,59	0,78	1,07	1,75	9,8	13,1
			0,31		0,11		3,7
6—12    >    ....	7	0,93	1,31	1,75	3,32	16,4	27,6
			0,55		0,52		9,0
1—2 years ....	7	1,05	1,66	3,63	5,40	21,9	47,3
			0,61		1,24		8,6

Table 2.  
*Enzymic Values in 32 Infants under 1 Year with Chronic Dyspepsia, as compared to Normal Children.*

Age	Number	Trypsin		Amylase		Lipase	
		Normal	Chron. dysp.	Normal	Chron. dysp.	Normal	Chron. dysp.
0—3 months	norm.: 2 chr. d.: 6	0,47 0,39	0,81 0,38	0,17 0,14	0,36 0,16	7,8 6,8	7,3 5,4
		0,30	0,17	0,10	0,01	5,7	4,0
3—6 months	norm.: 6 chr. d. 13	0,78 0,59	1,20 0,66	1,75 1,07	1,56 0,67	13,1 9,8	20,1 11,7
		0,31	0,26	0,11	0,25	3,7	2,1
6—12 months	norm.: 7 chr. d.: 13	1,31 0,93	1,45 0,67	3,32 1,75	1,41 0,80	27,6 16,4	27,0 14,5
		0,95	0,25	0,52	0,18	9,0	6,0

Table 3.  
*Enzymic Values in Children with Celiac Disease.*

Age	Number	Trypsin		Amylase		Lipase	
		Normal	Celiac.	Normal	Celiac.	Normal	Celiac.
1—2 years	norm.: 7 cel.: 10	1,05	0,70	3,33	2,43	21,9	14,1
		0,61	0,30	1,24	0,69	8,60	7,00

Table 4.  
*Enzymic Values in 4 Children with Pancreatic Fibrosis.*

Age	Number	Trypsin		Amylase		Lipase	
		Normal	Pancreatic fibrosis	Normal	Pancreatic fibrosis	Normal	Pancreatic fibrosis
0—3 months	norm.: 2 fibr.: 1	0,39	0,00	0,14	0,05	6,8	0,4
3—6 months	norm.: 6 fibr.: 3	0,59	0,00	1,07	trace	9,8	0,3
		0,00		0,00		0,0	

From the Pediatric Department, University Clinic at Rigshospitalet,  
Copenhagen.  
Head: Professor P. Plum.

### CONGENITAL CYSTIC FIBROSIS OF THE PANCREAS

By

HENNING ANDERSEN, CLAUS DUEHOLM and E. W. FLENSBORG  
(Denmark).

The material comprises 8 cases of congenital fibrosis of the pancreas, admitted to pediatric clinics in Copenhagen in 1945-48. Some of these cases have been published previously by Flensburg.

In 6 cases the diagnosis was verified by microscopy, in 2 cases by pancreatic enzyme analysis, and in one case by enzyme analysis and subsequent microscopy. Clinically 2 of these children presented meconium ileus, while the remaining 6 children have had dyspeptic symptoms and relapsing infections of the air passages, commencing within the first six months of life.

Of these children 6 died, while 2 are still living, respectively 12 and 18 months after the diagnosis was made. No special treatment was given in the first 5 cases; these children all died. The last 3 children were treated entirely with diet and pancreatin ad modum Dorothy Andersen. Of these children, 2 are living.

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### THE INCIDENCE OF RICKETS AND CRANIOTABES IN DENMARK DURING THE FIRST YEAR OF LIFE (Summary of Graphic Exhibition.)

By

O. ANDERSEN, A. ROTHE-MEYER and F. TUDVAD (Denmark).

During the fall of 1939 and the spring and fall of 1941 a total of 895 infants aged 2-12 months from the counties of *Holbæk* and *Hjørring* were investigated. The infants were spotted and summoned by investigator nurses for this special medical investigation, which comprised complete objective examination and roentgenograms of the wrists. A diagnosis of

*ricketts* was only accepted on the basis of pathological x-ray changes, while the diagnosis of *craniotabes* was based upon the palpatory method.

*Incidence:* As expected the autumnal series revealed only few cases of *ricketts* (7 out of 538), while the spring of 1941 rendered a larger number (80 out of 357). Among infants aged 2-4 months no *ricketts* was found, while the age period 6-13 months showed an almost uniform distribution of *ricketts* within the monthly groups.

*Craniotabes* was rare in the fall of 1939 (18 out of 328), more frequent in the fall of 1941 (45 out of 210) and had its highest incidence in the spring of 1941 (110 out of 357). The majority of cases occurred in the age group 3-7 months with rapidly decreasing incidence in later age groups. The different percentage of *craniotabes* found in the two fall investigations may well have been caused by two different medical examiners.

*Sex:* Among the 357 infants examined in the spring of 1941 boys showed a significantly higher incidence of *ricketts* (31.2 per cent) than girls (14.4 per cent). No such sex correlation could be demonstrated for *craniotabes*.

*Nutrition:* An analysis, based on the criterion whether human milk had been an essential part of the feeding for less or more than four months, revealed the fact, that *ricketts* occurs most frequently in infants fed on human milk for less than four months. *Craniotabes* did not exhibit any significant correlation to the investigated types of nutrition.

*Growth:* By a special analysis of the growth it could be shown for the age group 8-13 months, that the higher the speed of growth, the lower the incidence of *ricketts*. In infants under 6 months of age on the other hand the frequency of *craniotabes* is higher, the greater the speed of growth.

*Growth and nutrition:* By correlating the nutrition to the intensity of growth it was found that the growth intensity is highest in infants, that have been fed on human milk for the shortest period. Thus it is necessary to take both these factors into consideration in evaluating *ricketts* and *craniotabes*. An analysis based upon these points of view yielded the following conclusions.

In infants on identical feeding the incidence of *ricketts* is less among infants with high growth intensity than in infants growing more slowly. *Craniotabes* showed the opposite behaviour, the incidence being highest in rapidly growing infants.

On the other hand, in infants with identical growth intensity, the incidence of *ricketts* is the least in individuals that have been fed on human milk for a period of or above four months. This favourable effect of human milk could not be demonstrated for *craniotabes*.

In spite of the characteristic differences between *ricketts* and *craniotabes* here reported, this investigation does not refute the conception of *craniotabes* as an integrating part of *ricketts*.

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#### NEONATAL OSTEOMYELITIS

By

TORBJØRN BENNIKE (Denmark).

Altogether 25 cases of osteomyelitis within the first six weeks of life, 14 boys and 11 girls, are collected from 5 pediatric and 2 surgical clinics in Copenhagen, admitted during the period of 1933 to 1948.

In 15 of these cases the etiology was infection with *staph. aureus* while hemolytic streptococci were found only in 3 cases. In 4 cases no cultures were made.

The most frequent localisation was the proximal end of the femur and humerus; then, the pelvis, phalanges and tibia. Purulent "osteomyelitic arthritis" arose in 15 patients, most often in the hip joint.

In one case no therapeutic measures were employed; 8 patients were treated surgically alone, most often merely with incision of the abscess, while 16 patients were given chemotherapy (penicillin in 4 cases, sulfa-preparations in 7, and both remedies in 5).

Altogether 7 patients (28 %) died, most often from septic complications. Of the 13 patients who were given sufficient chemotherapy in the first week of the disease, none died.

In 12 patients the morbid processes were of more chronic

character: fistulous osteomyelitis with sequestration in 6 cases, protracted roentgenographic changes in 4, and subsequent discharge of small sequesters in 2.

Follow-up examination, from 10 months to 10 years (on an average 5 years) later showed considerable deformity in 11 cases.

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*From the Pediatric Department at the Copenhagen County Hospital, Hellerup.*  
*Head: P. W. Bræstrup, M. D.*

**SURVEY OF SYMPTOMS AND TREATMENT OF SEVERE OBTURATING TRACHEOBRONCHITIS — ON THE BASIS OF 16 CASES**

By  
**P. W. BRÆSTRUP (Denmark).**

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*From the Pediatric Department, University Clinic at Rigshospitalet, Copenhagen.*  
*Head: Professor P. Plum.*

**ASTHMA IN CHILDREN. SURVEY OF CLINICAL ASPECTS, ETIOLOGY, TREATMENT AND PROGNOSIS**

By  
**E. WINGE FLENSBORG, G. NEERBORG and T. SAMSØE-JENSEN (Denmark).**

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*From the Pediatric Department at the Copenhagen County Hospital, Hellerup.*  
*Head: P. W. Bræstrup, M. D.*

**STATISTICAL ACCOUNT OF THE EFFECT OF LOCUST-BEAN POWDER ON DYSPEPSIA IN INFANTS**

By  
**ANNA FRANDSEN (Denmark).**

In diagrams an account is given of the routine treatment with the locust-bean preparation "Arobon" employed in the

Pediatric Department of the Copenhagen County Hospital and of the therapeutic results obtained in altogether 93 cases of infantile dyspepsia. This material includes:

56 cases of acute dyspepsia in infancy (3 weeks-10 months), 34 non-intoxicated and 22 intoxicated cases with serum bicarbonate < 18 mil. equiv.,

10 cases of acute malignant gastroenteritis (13 days-2½ months) and

18 cases of moderate acute dyspepsia in infants (5 months-2 years), all treated with Arobon given as 5 % addition to other special diet or ordinary diet. Besides,

9 cases of chronic dyspepsia (3-18 months) were treated tentatively with 5 % Arobon addition to other diet.

Rapid and favorable effect was observed in the acute cases, no definite or lasting effect in the chronic cases.

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*From the Pediatric Department at the Copenhagen County Hospital, Hellerup.*

*Head: P. W. Bræstrup, M. D.*

#### CASE OF VITAMIN D-RESISTANT RICKETS

By

J. KOCH (Denmark).

A report is given of a severe florid case of rickets in a girl, 22 months old, in whom the treatment with 3.500 I. U. of vitamin D for 2 months had been without any effect.

Treatment with 50.000 international units, increasing to 300.000 units gave commencing healing after 3 weeks, but complete roentgenographic healing only after 5 months.

At first the serum phosphorus was 2.2 mg%, and it remained typically subnormal — about 3,0 mg% — even after clinical and roentgenographic healing was obtained.

The serum phosphatase was at first high, rising in the first 2 months of the treatment, and it continued being markedly increased after 5 months' treatment.

Serum calcium kept constantly within the normal limits.

It is emphasized that the intensive vitamin D therapy should not be carried through without frequent examination of the serum calcium and calcium output with the urine.

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*From the Pediatric Clinic at Kronprinsessan Lovisa's Children's Hospital, Stockholm.*

*Head: Professor A. Lichtenstein.*

#### OXYGEN INCUBATOR (LICHENSTEIN'S MODEL)

By  
A. LICHTENSTEIN (Sweden).

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*From the Pediatric Clinic at Kronprinsessan Lovisa's Children's Hospital, Stockholm.*

*Head: Professor A. Lichtenstein.*

#### PEDIATRIC CARDIOLOGY

By  
EDGAR MANNHEIMER and E. ULFSPARRE (Sweden).

This exhibition aims to throw some light on the clinical value of such cardiological methods of examination as electrocardiography, phonocardiography, venous pulse registration, hypoxia tolerance, angiocardiology and catheterization of the heart, with special reference to the diagnosis of congenital heart lesions in children.

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#### EMPLOYMENT OF ELECTROENCEPHALOGRAPHY IN PEDIATRICS

By  
K.-A. MELIN (Sweden).

This exhibition aims merely to illustrate the routine employment of electroencephalography in a pediatric clinic.

*From the Pediatric Department at the Copenhagen County  
Hospital, Hellerup.  
Head: P. W. Bræstrup, M. D.*

FRACTIONATED SERUM LIPOID ANALYSIS IN CHILDREN

By  
ERIK WAMBERG (Denmark).

(Published in »Nordisk Medicin« 41:262, 1949.)

**GENERAL MEETING OF THE NORTHERN PEDIATRIC  
ASSOCIATION**

**on August 16, 1948.**

An account of the financial status of the association was given by the former Secretary General, Docent C. E. Räihä, Finland.

After the retirement of Dr. C. Friderichsen, Denmark, Professor Arvo Ylppö, Finland, and Professor A. Lichtenstein, Sweden, the following new board were elected:

***Denmark:***

Prof. P. Plum,  
Prof. Oluf Andersen,  
Dr. Paul Drucker, secretary,  
Dr. Arne Rothe-Meyer, substitute.

***Finland:***

Prof. V. Rantasalo,  
Docent C. E. Räihä,  
Prof. Toivo Salmi, secretary,  
Docent Paavo Heiniö, substitute.

***Norway:***

Prof. Leif Salomonsen,  
Dr. L. Stoltenberg,  
Dr. Arne Njå, secretary,  
Dr. Alfred Sundal, substitute.

***Sweden:***

Prof. C. Gyllenswärd,  
Prof. A. Wallgren,  
Prof. Sture Siwe,  
Dr. Justus Ström, secretary and substitute.

Revisors: Drs. Lahdensuu, Finland, and Gjørup, Denmark, together with the substitutes Dr. Odd Marvet, Norway, and Prof. Malmberg, Sweden.

At the motion made by the board, the general meeting decided that the next congress was to take place in Stockholm in June, 1951. Prof. A. Lichtenstein was elected president of the next congress.

Before the President, Dr. C. Friderichsen closed the congress, it was voted to make Prof. C. E. Bloch an honorary member of the association.



## INDEX

Bold-type figures refer to papers read, ordinary types to contributions to discussions and to the congressional exhibition.

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